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(54) Title: IRREVERSIBLE SELECTIVE ANDROGEN RECEPTOR MODULATORS AND METHODS OF USE THEREOF

(57) **Abstract:** In one embodiment, this invention provides a class of androgen receptor targeting agents (ARTA). The agents define a new subclass of compounds, which are selective androgen receptor modulators (SARM). The SARM compounds have unexpected antiandrogenic activity of a nonsteroidal ligand for the androgen receptor. In one embodiment, the SARM compounds bind irreversibly to the androgen receptor. In another embodiment, the SARM compounds are androgen receptor antagonists which bind irreversibly to the androgen receptor. In another embodiment, the SARM compounds are alkylating agents. The SARM compounds, either alone or as a composition, are useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with Androgen Decline in Aging Male (ADAM), such as fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, anemia, obesity, sarcopenia, osteopenia, osteoporosis, benign prostate hyperplasia, alterations in mood and cognition and prostate cancer; c) treatment of conditions associated with Androgen Decline in Female (ADIF), such as sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian cancer; d) treatment and/or prevention of acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; g) decreasing the incidence of, halting or causing a regression of prostate cancer; and/or h) inducing apoptosis in a cancer cell.

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**IRREVERSIBLE SELECTIVE ANDROGEN RECEPTOR MODULATORS  
AND METHODS OF USE THEREOF**

5                                   **GOVERNMENT INTEREST STATEMENT**

[0001] This invention was made in whole or in part with government support under grant number R29 CA068096 awarded by the National Cancer Institute, National Institute of Health, and under grant number R15 HD35329, awarded by the National Institute of Child Health and Human Development, National Institute of Health. The  
10       government may have certain rights in the invention.

**FIELD OF INVENTION**

[0002] The present invention relates to androgen receptor targeting agents (ARTA) which demonstrate antiandrogenic activity of a nonsteroidal ligand for the androgen  
15       receptor, and/or which bind irreversibly to the androgen receptor. The agents define a new subclass of compounds, which are selective androgen receptor modulators (SARMs) useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with Androgen Decline in Aging Male (ADAM); c) treatment of conditions associated with Androgen Decline in Female  
20       (ADIF); d) treatment and/or prevention of acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; g) decreasing the incidence of, halting or causing a regression of prostate cancer; and/or h) inducing apoptosis in a cancer cell.

25                                   **BACKGROUND OF THE INVENTION**

[0003] The androgen receptor ("AR") is a ligand-activated transcriptional regulatory protein that mediates induction of male sexual development and function through its activity with endogenous androgens. Androgens are generally known as the male sex hormones. The androgenic hormones are steroids which are produced in the body by the  
30       testes and the cortex of the adrenal gland or can be synthesized in the laboratory. Androgenic steroids play an important role in many physiologic processes, including the development and maintenance of male sexual characteristics such as muscle and bone mass, prostate growth, spermatogenesis, and the male hair pattern (Matsumoto,

Endocrinol. Met. Clin. N. Am. 23:857-75 (1994)). The endogenous steroidal androgens include testosterone and dihydrotestosterone ("DHT"). Testosterone is the principal steroid secreted by the testes and is the primary circulating androgen found in the plasma of males. Testosterone is converted to DHT by the enzyme 5 alpha-reductase in many peripheral tissues. DHT is thus thought to serve as the intracellular mediator for most androgen actions (Zhou, et al., Molec. Endocrinol. 9:208-18 (1995)). Other steroidal androgens include esters of testosterone, such as the cypionate, propionate, phenylpropionate, cyclopentylpropionate, isocarporate, enanthate, and decanoate esters, and other synthetic androgens such as 7-Methyl-Nortestosterone ("MENT") and its acetate ester (Sundaram et al., "7 Alpha-Methyl-Nortestosterone(MENT): The Optimal Androgen For Male Contraception," Ann. Med., 25:199-205 (1993) ("Sundaram")). Because the AR is involved in male sexual development and function, the AR is a likely target for effecting male contraception or other forms of hormone replacement therapy.

[0004] Worldwide population growth and social awareness of family planning have stimulated a great deal of research in contraception. Contraception is a difficult subject under any circumstance. It is fraught with cultural and social stigma, religious implications, and, most certainly, significant health concerns. This situation is only exacerbated when the subject focuses on male contraception. Despite the availability of suitable contraceptive devices, historically, society has looked to women to be responsible for contraceptive decisions and their consequences. Although concern over sexually transmitted diseases has made men more aware of the need to develop safe and responsible sexual habits, women still often bear the brunt of contraceptive choice. Women have a number of choices, from temporary mechanical devices such as sponges and diaphragms to temporary chemical devices such as spermicides. Women also have at their disposal more permanent options, such as physical devices including IUDs and cervical caps as well as more permanent chemical treatments such as birth control pills and subcutaneous implants. However, to date, the only options available for men include the use of condoms and vasectomy. Condom use, however is not favored by many men because of the reduced sexual sensitivity, the interruption in sexual spontaneity, and the significant possibility of pregnancy caused by breakage or misuse. Vasectomies are also not favored. If more convenient methods of birth control were available to men,

particularly long-term methods which require no preparative activity immediately prior to a sexual act, such methods could significantly increase the likelihood that men would take more responsibility for contraception.

5 [0005] Administration of the male sex steroids (e.g., testosterone and its derivatives) has shown particular promise in this regard due to the combined gonadotropin-suppressing and androgen-substituting properties of these compounds (Steinberger et al., "Effect of Chronic Administration of Testosterone Enanthate on Sperm Production and Plasma Testosterone, Follicle Stimulating Hormone, and Luteinizing Hormone Levels: A Preliminary Evaluation of a Possible Male Contraceptive, Fertility and Sterility 28:1320-10 28 (1977)). Chronic administration of high doses of testosterone completely abolishes sperm production (azoospermia) or reduces it to a very low level (oligospermia). The degree of spermatogenic suppression necessary to produce infertility is not precisely known. However, a recent report by the World Health Organization showed that weekly 15 intramuscular injections of testosterone enanthate result in azoospermia or severe oligospermia (i.e., less than 3 million sperm per ml) and infertility in 98% of men receiving therapy (World Health Organization Task Force on Methods And Regulation of Male Fertility, "Contraceptive Efficacy of Testosterone-Induced Azoospermia and Oligospermia in Normal Men," Fertility and Sterility 65:821-29 (1996)).

20

[0006] A variety of testosterone esters have been developed which are more slowly absorbed after intramuscular injection and thus result in greater androgenic effect. Testosterone enanthate is the most widely used of these esters. While testosterone enanthate has been valuable in terms of establishing the feasibility of hormonal agents 25 for male contraception, it has several drawbacks, including the need for weekly injections and the presence of supraphysiologic peak levels of testosterone immediately following intramuscular injection (Wu, "Effects of Testosterone Enanthate in Normal Men: Experience From a Multicenter Contraceptive Efficacy Study," Fertility and Sterility 65:626-36 (1996)).

30

[0007] Steroidal ligands which bind the AR and act as androgens (e.g. testosterone enanthate) or as antiandrogens (e.g. cyproterone acetate) have been known for many



years and are used clinically (Wu 1988). Although nonsteroidal antiandrogens are in clinical use for hormone-dependent prostate cancer, nonsteroidal androgens have not been reported. For this reason, research on male contraceptives has focused solely on steroidal compounds.

5

[0008] Prostate cancer is one of the most frequently occurring cancers among men in the United States, with hundreds of thousands of new cases diagnosed each year. Unfortunately, over sixty percent of newly diagnosed cases of prostate cancer are found to be pathologically advanced, with no cure and a dismal prognosis. One approach to  
10 this problem is to find prostate cancer earlier through screening programs and thereby reduce the number of advanced prostate cancer patients. Another strategy, however, is to develop drugs to prevent prostate cancer. One third of all men over 50 years of age have a latent form of prostate cancer that may be activated into the life-threatening clinical prostate cancer form. The frequency of latent prostatic tumors has been shown to  
15 increase substantially with each decade of life from the 50s (5.3-14%) to the 90s (40-80%). The number of people with latent prostate cancer is the same across all cultures, ethnic groups, and races, yet the frequency of clinically aggressive cancer is markedly different. This suggests that environmental factors may play a role in activating latent prostate cancer. Thus, the development of treatment and preventative strategies against  
20 prostate cancer may have the greatest overall impact both medically and economically against prostate cancer.

[0009] Osteoporosis is a systemic skeletal disease, characterized by low bone mass and deterioration of bone tissue, with a consequent increase in bone fragility and  
25 susceptibility to fracture. In the U.S., the condition affects more than 25 million people and causes more than 1.3 million fractures each year, including 500,000 spine, 250,000 hip and 240,000 wrist fractures annually. Hip fractures are the most serious consequence of osteoporosis, with 5-20% of patients dying within one year, and over 50% of survivors being incapacitated. The elderly are at greatest risk of osteoporosis, and the  
30 problem is therefore predicted to increase significantly with the aging of the population. Worldwide fracture incidence is forecasted to increase three-fold over the next 60 years, and one study estimated that there will be 4.5 million hip fractures worldwide in 2050.

[00010] Women are at greater risk of osteoporosis than men. Women experience a sharp acceleration of bone loss during the five years following menopause. Other factors that increase the risk include smoking, alcohol abuse, a sedentary lifestyle and low calcium intake. However, osteoporosis also occurs frequently in males. It is well established that the bone mineral density of males decrease with age. Decreased amounts of bone mineral content and density correlates with decreased bone strength, and predisposes to fracture. The molecular mechanisms underlying the pleiotropic effects of sex-hormones in non-reproductive tissues are only beginning to be understood, but it is clear that physiologic concentrations of androgens and estrogens play an important role in maintaining bone homeostasis throughout the life-cycle. Consequently, when androgen or estrogen deprivation occurs there is a resultant increase in the rate of bone remodeling that tilts the balance of resorption and formation to the favor of resorption that contributes to the overall loss of bone mass. In males, the natural decline in sex-hormones at maturity (direct decline in androgens as well as lower levels of estrogens derived from peripheral aromatization of androgens) is associated with the frailty of bones. This effect is also observed in males who have been castrated.

[00011] Androgen decline in the aging male (ADAM) refers to a progressive decrease in androgen production, common in males after middle age. The syndrome is characterized by alterations in the physical and intellectual domains that correlate with and can be corrected by manipulation of the androgen milieu. ADAM is characterized biochemically by a decrease not only in serum androgen, but also in other hormones, such as growth hormone, melatonin and dehydroepiandrosterone. Clinical manifestations include fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, obesity, sarcopenia, osteopenia, benign prostate hyperplasia, anemia, alterations in mood and cognition and prostate cancer.

[00012] Androgen Deficiency in Female (ADIF) refers to a variety of hormone-related conditions including, common in females after middle age. The syndrome is characterized by sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia,

osteopenia, osteoporosis, alterations in cognition and mood, anemia, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian cancer.

[00013] Muscle wasting refers to the progressive loss of muscle mass and/or to the  
5 progressive weakening and degeneration of muscles, including the skeletal or voluntary  
muscles, which control movement, cardiac muscles, which control the heart  
(cardiomyopathies), and smooth muscles. Chronic muscle wasting is a chronic  
condition (i.e. persisting over a long period of time) characterized by progressive loss of  
muscle mass, weakening and degeneration of muscle. The loss of muscle mass that  
10 occurs during muscle wasting can be characterized by a muscle protein breakdown or  
degradation. Protein degradation occurs because of an unusually high rate of protein  
degradation, an unusually low rate of protein synthesis, or a combination of both.  
Protein degradation, whether caused by a high degree of protein degradation or a low  
degree of protein synthesis, leads to a decrease in muscle mass and to muscle wasting.  
15 Muscle wasting is associated with chronic, neurological, genetic or infectious  
pathologies, diseases, illnesses or conditions. These include Muscular Dystrophies such  
as Duchenne Muscular Dystrophy and Myotonic Dystrophy; Muscle Atrophies such as  
Post-Polio Muscle Atrophy (PPMA); Cachexias such as Cardiac Cachexia, AIDS  
Cachexia and Cancer Cachexia, malnutrition, Leprosy, Diabetes, Renal Disease, Chronic  
20 Obstructive Pulmonary Disease (COPD), Cancer, end stage Renal failure, Emphysema,  
Osteomalacia, HIV Infection, AIDS, and Cardiomyopathy. In addition, other  
circumstances and conditions are linked to and can cause muscle wasting. These include  
chronic lower back pain, advanced age, central nervous system (CNS) injury, peripheral  
nerve injury, spinal cord injury, chemical injury, central nervous system (CNS) damage,  
25 peripheral nerve damage, spinal cord damage, chemical damage, burns, disuse  
deconditioning that occurs when a limb is immobilized, long term hospitalization due to  
illness or injury, and alcoholism. Muscle wasting, if left unabated, can have dire health  
consequences. For example, the changes that occur during muscle wasting can lead to a  
weakened physical state that is detrimental to an individual's health, resulting in  
30 increased susceptibility to infection, poor performance status and susceptibility to injury.

[00014] New innovative approaches are urgently needed at both the basic science and clinical levels to develop compounds which are useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with Androgen Decline in Aging Male (ADAM), such as fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, anemia, obesity, sarcopenia, osteopenia, osteoporosis, benign prostate hyperplasia, alterations in mood and cognition and prostate cancer; c) treatment of conditions associated with ADIF, such as sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian cancer; d) treatment and/or prevention of acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; g) decreasing the incidence of, halting or causing a regression of prostate cancer; and/or h) inducing apoptosis in a cancer cell.

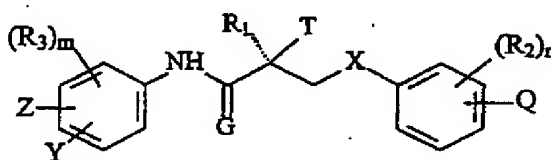
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#### SUMMARY OF THE INVENTION

[00015] In one embodiment, this invention provides androgen receptor targeting agents (ARTA). The agents define a new subclass of compounds, which are selective androgen receptor modulators (SARM). The SARM compounds have unexpected antiandrogenic activity of a nonsteroidal ligand for the androgen receptor. In one embodiment, the SARM compounds bind irreversibly to the androgen receptor. In another embodiment, the SARM compounds are androgen receptor antagonists which bind irreversibly to the androgen receptor. In another embodiment, the SARM compounds are alkylating agents. The SARM compounds, either alone or as a composition, are useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with Androgen Decline in Aging Male (ADAM), such as fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, anemia, obesity, sarcopenia, osteopenia, osteoporosis, benign prostate hyperplasia, alterations in mood and cognition and prostate cancer; c) treatment of conditions associated with Androgen Decline in Female (ADIF), such as sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity,

endometriosis, breast cancer, uterine cancer and ovarian cancer; d) treatment and/or prevention of acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; g) decreasing the incidence of, halting or causing a regression of prostate cancer; and/or h) inducing apoptosis in a cancer cell.

[00016] In one embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula I:



I

X is a bond, O, CH<sub>2</sub>, NH, S, Se, PR, NO or NR;

G is O or S;

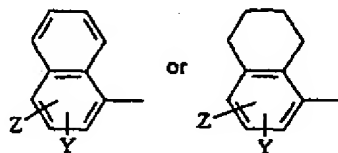
T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH;

R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;

R<sub>2</sub> is F, Cl, Br, I, CH<sub>3</sub>, CF<sub>3</sub>, OH, CN, NO<sub>2</sub>, NHCOCH<sub>3</sub>, NHCOCF<sub>3</sub>, NHCOR, alkyl, arylalkyl, OR, NH<sub>2</sub>, NHR, NR<sub>2</sub>, SR;

R<sub>3</sub> is F, Cl, Br, I, CN, NO<sub>2</sub>, COR, COOH, CONHR, CF<sub>3</sub>, SnR<sub>3</sub>, or R<sub>3</sub> together with the benzene ring to which it is attached forms a fused ring system represented by the structure:



Z is NO<sub>2</sub>, CN, COR, COOH, or CONHR;

Y is CF<sub>3</sub>, F, Br, Cl, I, CN, or SnR<sub>3</sub>;

Q is SCN, NCS, OCN, or NCO;

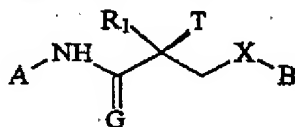
n is an integer of 1-4; and

m is an integer of 1-3.

[00017] In another embodiment, the present invention provides an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or  
 5 N-oxide of the compound of formula I, or any combination thereof.

[00018] In one embodiment, G in compound I is O. In another embodiment, X in compound I is O. In another embodiment, T in compound I is OH. In another embodiment, R<sub>1</sub> in compound I is CH<sub>3</sub>. In another embodiment, Z in compound I is NO<sub>2</sub>. In another embodiment, Z in compound I is CN. In another embodiment, Y in  
 10 compound I is CF<sub>3</sub>. In another embodiment, Q in compound I is NCS. In another embodiment, Q in compound I is in the para position. In another embodiment, Z in compound I is in the para position. In another embodiment, Y in compound I is in the meta position. In another embodiment, G in compound I is O, T is OH, R<sub>1</sub> is CH<sub>3</sub>, X is  
 15 O, Z is NO<sub>2</sub>, Y is CF<sub>3</sub>, and Q is NCS.

[00019] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula II:



II

20

wherein

X is a bond, O, CH<sub>2</sub>, NH, S, Se, PR, NO or NR;

G is O or S;

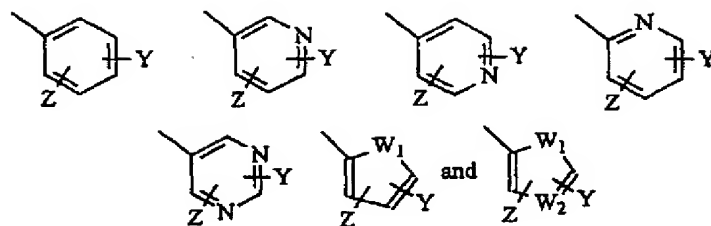
R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;

T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR;

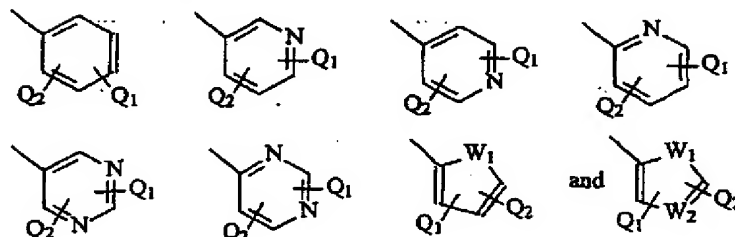
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R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH;

A is a ring selected from:



B is a ring selected from:



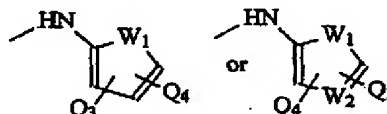
wherein A and B cannot simultaneously be a benzene ring;

Z is  $\text{NO}_2$ , CN, COOH, COR, NHCOR or CONHR;

Y is  $\text{CF}_3$ , F, I, Br, Cl, CN  $\text{CR}_3$  or  $\text{SnR}_3$ ;

$\text{Q}_1$  is NCS, SCN, NCO or OCN;

$\text{Q}_2$  is a hydrogen, alkyl, halogen,  $\text{CF}_3$ , CN  $\text{CR}_3$ ,  $\text{SnR}_3$ ,  $\text{NR}_2$ ,  $\text{NHCOCH}_3$ ,  $\text{NHCOCF}_3$ , NHCOR, NHCONHR,  $\text{NHCOOR}$ , OCONHR, CONHR,  $\text{NHCSCH}_3$ ,  $\text{NHCSCF}_3$ ,  $\text{NHCSR}$ ,  $\text{NHSO}_2\text{CH}_3$ ,  $\text{NHSO}_2\text{R}$ , OR, COR, OCOR,  $\text{OSO}_2\text{R}$ ,  $\text{SO}_2\text{R}$ , SR,



$\text{Q}_3$  and  $\text{Q}_4$  are independently of each other a hydrogen, alkyl, halogen,  $\text{CF}_3$ , CN  $\text{CR}_3$ ,  $\text{SnR}_3$ ,  $\text{NR}_2$ ,  $\text{NHCOCH}_3$ ,  $\text{NHCOCF}_3$ , NHCOR, NHCONHR,  $\text{NHCOOR}$ , OCONHR, CONHR,  $\text{NHCSCH}_3$ ,  $\text{NHCSCF}_3$ ,  $\text{NHCSR}$ ,  $\text{NHSO}_2\text{CH}_3$ ,  $\text{NHSO}_2\text{R}$ , OR, COR, OCOR,  $\text{OSO}_2\text{R}$ ,  $\text{SO}_2\text{R}$  or SR;

$\text{W}_1$  is O, NH, NR, NO or S; and

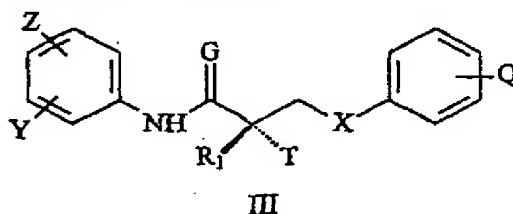
$\text{W}_2$  is N or NO.

[00020] In another embodiment, the present invention provides an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula II, or any combination thereof.

[00021] In one embodiment, G in compound II is O. In another embodiment, X in compound II is O. In another embodiment, T in compound II is OH. In another embodiment, R<sub>1</sub> in compound II is CH<sub>3</sub>. In another embodiment, Z in compound II is NO<sub>2</sub>. In another embodiment, Z in compound II is CN. In another embodiment, Y in compound II is CF<sub>3</sub>. In another embodiment, Q<sub>1</sub> in compound II is NCS. In another embodiment, Q<sub>1</sub> in compound II is in the para position. In another embodiment, Z in compound II is in the para position. In another embodiment, Y in compound II is in the meta position. In another embodiment, G in compound II is O, T is OH, R<sub>1</sub> is CH<sub>3</sub>, X is O, Z is NO<sub>2</sub>, Y is CF<sub>3</sub>, and Q<sub>1</sub> is NCS.

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[00022] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula III:



15

wherein

X is a bond, O, CH<sub>2</sub>, NH, S, Se, PR, NO or NR;

G is O or S;

T is OH, OR, -NHCOCH<sub>3</sub>, or NHCORZ is NO<sub>2</sub>, CN, COOH, COR, NHCOR or CONHR;Y is CF<sub>3</sub>, F, I, Br, Cl, CN, CR<sub>3</sub> or SnR<sub>3</sub>;

20

Q is SCN, NCS, OCN, or NCO;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH; and

R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>.

25

[00023] In another embodiment, the present invention provides an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula III, or any combination thereof.

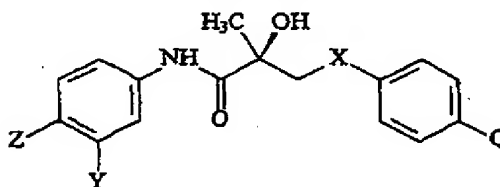
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[00024] In one embodiment, G in compound III is O. In another embodiment, X in compound III is O. In another embodiment, T in compound III is OH. In another



embodiment,  $R_1$  in compound III is  $\text{CH}_3$ . In another embodiment, Z in compound III is  $\text{NO}_2$ . In another embodiment, Z in compound III is  $\text{CN}$ . In another embodiment, Y in compound III is  $\text{CF}_3$ . In another embodiment, Q in compound III is  $\text{NCS}$ . In another embodiment, Q in compound III is in the para position. In another embodiment, Z in compound III is in the para position. In another embodiment, Y in compound III is in the meta position. In another embodiment, G in compound III is O, T is OH,  $R_1$  is  $\text{CH}_3$ , X is O, Z is  $\text{NO}_2$ , Y is  $\text{CF}_3$ , and Q is  $\text{NCS}$ .

[00025] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula IV:



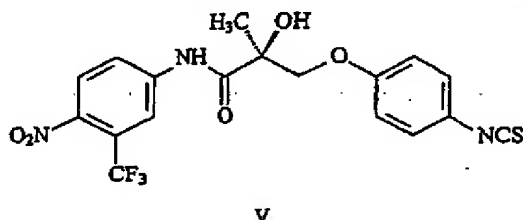
IV

wherein X is a bond, O,  $\text{CH}_2$ , NH, S, Se, PR, NO or NR;  
 Z is  $\text{NO}_2$ , CN, COOH, COR, NHCOR or CONHR;  
 Y is  $\text{CF}_3$ , F, I, Br, Cl, CN,  $\text{CR}_3$  or  $\text{SnR}_3$ ;  
 Q is SCN, NCS, OCN, or NCO; and  
 R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl,  $\text{CH}_2\text{F}$ ,  $\text{CHF}_2$ ,  $\text{CF}_3$ ,  $\text{CF}_2\text{CF}_3$ , aryl, phenyl, halogen, alkenyl or OH.

[00026] In another embodiment, the present invention provides an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula IV, or any combination thereof.

[00027] In one embodiment, X in compound IV is O. In another embodiment, Z in compound IV is  $\text{NO}_2$ . In another embodiment, Z in compound IV is CN. In another embodiment, Y in compound IV is  $\text{CF}_3$ . In another embodiment, Q in compound IV is NCS.

[00028] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula V, and/or an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide, or any combination thereof.



[00029] In one embodiment, the SARM compound of any of formulas I-V is an androgen receptor antagonist. In another embodiment, the SARM compound of any of formulas I-V binds irreversibly to an androgen receptor. In another embodiment, the SARM compound of any of formulas I-V is an androgen receptor antagonist which binds irreversibly to an androgen receptor. In another embodiment, the SARM compound of any of formulas I-V is an alkylating agent.

[00030] In one embodiment, the present invention provides a composition comprising the selective androgen receptor modulator compound of any of formulas I-V and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof.

[00031] In another embodiment, the present invention provides a pharmaceutical composition comprising the selective androgen receptor modulator compound of any of formulas I-V and/or its analog, derivative, isomer, metabolite, pharmaceutical product, hydrate, N-oxide or any combination thereof; and a suitable carrier or diluent.

[00032] In one embodiment, the present invention further provides a method of binding a selective androgen receptor modulator compound to an androgen receptor, comprising the step of contacting the androgen receptor with the selective androgen receptor modulator compound of any of formulas I-V, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to bind the selective androgen receptor modulator compound to the androgen receptor.

[00033] In another embodiment, the present invention further provides a method of irreversibly binding a selective androgen receptor modulator compound to an androgen receptor, comprising the step of contacting the androgen receptor with the selective  
5 androgen receptor modulator compound of any of formulas I-V, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to irreversibly bind the selective androgen receptor modulator compound to the androgen receptor.

10 [00034] In another embodiment, the present invention further provides a method of alkylating an androgen receptor, comprising the step of contacting the androgen receptor with the selective androgen receptor modulator compound of any of formulas I-V, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount  
15 effective to alkylate the androgen receptor.

[00035] In another embodiment, the present invention provides a method of suppressing spermatogenesis in a subject, comprising the step of contacting an androgen receptor of the subject with the selective androgen receptor modulator compound of any of formulas  
20 I-V and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to suppress sperm production.

[00036] In another embodiment, the present invention provides a method of  
25 contraception in a male subject, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of formulas I-V and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to suppress sperm production in the subject, thereby effecting contraception in the subject.

30 [00037] In another embodiment, the present invention further provides a method of hormone therapy, comprising the step of contacting an androgen receptor of a subject

with the selective androgen receptor modulator compound of any of any of formulas I-V and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to bind the selective androgen receptor modulator compound to the androgen  
5 receptor and effect a change in an androgen-dependent condition.

[00038] In another embodiment, the present invention provides a method of hormone replacement therapy comprising the step of contacting an androgen receptor of a subject with the selective androgen receptor modulator compound of any of formulas I-V and/or  
10 its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to effect a change in an androgen-dependent condition.

[00039] In another embodiment, the present invention further provides a method of  
15 treating a subject having a hormone related condition, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of any of formulas I-V and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to bind the selective androgen receptor  
20 modulator compound to the androgen receptor and effect a change in an androgen-dependent condition.

[00040] In another embodiment, the present invention further provides a method of  
25 treating a subject suffering from prostate cancer, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of formulas I-V, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to treat prostate cancer in the subject.

30 [00041] In another embodiment, the present invention provides a method of preventing prostate cancer in a subject, comprising the step of administering to the subject the selective androgen receptor modulator compound of formulas I-V and/or its analog,

derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to prevent prostate cancer in the subject.

5 [00042] In another embodiment, the present invention further provides a method of delaying the progression of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of any of formulas I-V, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate,  
10 N-oxide or any combination thereof, in an amount effective to delay the progression of prostate cancer in the subject.

[00043] In another embodiment, the present invention further provides a method of preventing the recurrence of prostate cancer in a subject suffering from prostate cancer,  
15 comprising the step of administering to the subject the selective androgen receptor modulator compound of any of any of formulas I-V, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to prevent the recurrence of prostate cancer in the subject.

20

[00044] In another embodiment, the present invention provides a method of treating the recurrence of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of any of formulas I-V, and/or its analog, derivative, isomer, metabolite,  
25 pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to treat the recurrence of prostate cancer in the subject.

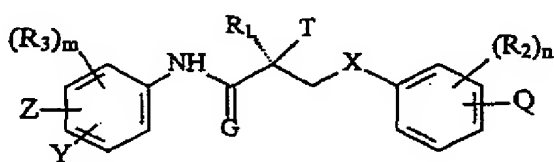
[00045] In another embodiment, the present invention provides a method of treating a  
30 dry eye condition in a subject suffering from dry eyes, comprising the step of administering to said subject the selective androgen receptor modulator compound of formulas I-V and/or its analog, derivative, isomer, metabolite, pharmaceutically

acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to treat dry eyes in the subject.

[00046] In another embodiment, the present invention provides a method of preventing a dry eye condition in a subject, comprising the step of administering to said subject the selective androgen receptor modulator compound of formulas I-V and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to prevent dry eyes in the subject.

[00047] In another embodiment, the present invention provides a method of inducing apoptosis in a prostate cancer cell, comprising the step of contacting the cell with the selective androgen receptor modulator compound of any of any of formulas I-V, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to induce apoptosis in the cancer cell.

[00048] In another embodiment, the present invention provides process for preparing a selective androgen receptor modulator (SARM) compound represented by the structure of formula I:



I

wherein X is a O, NH, S, Se, PR, or NR;

G is O or S;

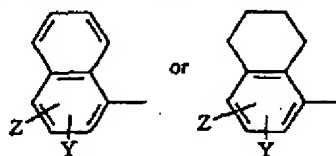
T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH;

R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;

$R_2$  is F, Cl, Br, I,  $CH_3$ ,  $CF_3$ , OH, CN,  $NO_2$ ,  $NHCOCH_3$ ,  $NHCOCF_3$ ,  $NHCOR$ , alkyl, arylalkyl, OR,  $NH_2$ ,  $NHR$ ,  $NR_2$ , SR;

$R_3$  is F, Cl, Br, I, CN,  $NO_2$ , COR, COOH, CONHR,  $CF_3$ ,  $SnR_3$ , or  $R_3$  together with the benzene ring to which it is attached forms a fused ring system represented by the structure:



Z is  $NO_2$ , CN, COR, COOH, or CONHR;

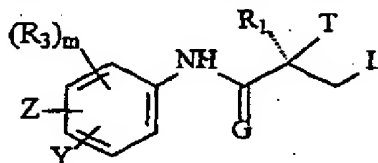
Y is  $CF_3$ , F, Br, Cl, I, CN, or  $SnR_3$ ;

Q is SCN, NCS, OCN, or NCO;

n is an integer of 1-4; and

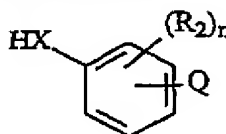
m is an integer of 1-3;

the process comprising the step of coupling a compound of formula VIII:



VIII

wherein Z, Y, G,  $R_1$ , T,  $R_3$  and m are as defined above and L is a leaving group, with a compound of formula IX:

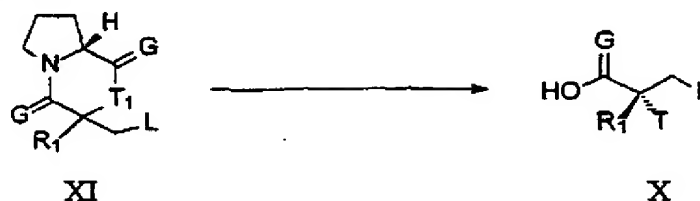


IX

wherein Q, X  $R_2$  and n are as defined above.

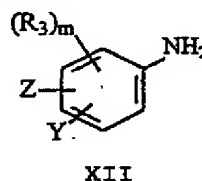
[00049] In one embodiment, the coupling step is carried out in the presence of a base. In another embodiment, the leaving group L is Br. In another embodiment, the compound of formula VIII is prepared by

- i) preparing a compound of formula X by ring opening of a cyclic compound of formula XI

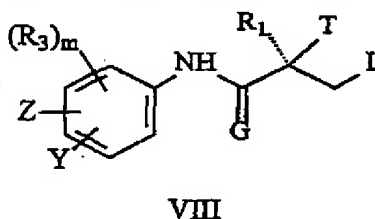


wherein L, R<sub>1</sub>, G and T are as defined above, and T<sub>1</sub> is O or NH; and

- ii) reacting an amine of formula XII:

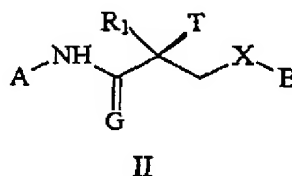


wherein Z, Y, R<sub>3</sub> and m are as defined above, with the compound of formula X, in the presence of a coupling reagent, to produce the compound of formula VIII.



[00050] In one embodiment, step (a) is carried out in the presence of HBr. In another embodiment, the process further comprises the step of converting the selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

[00051] In another embodiment, the present invention provides process for preparing a selective androgen receptor modulator (SARM) compound represented by the structure of formula II:





wherein X is O, NH, S, Se, PR, or NR;

G is O or S;

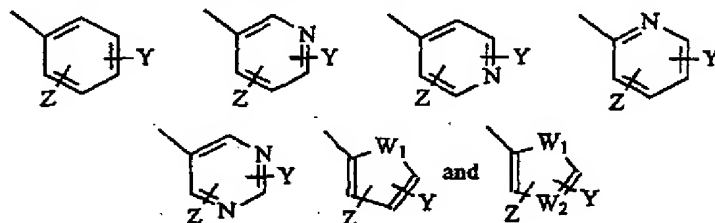
R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;

T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR;

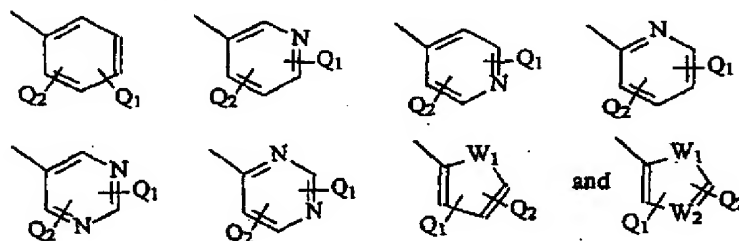
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R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH;

A is a ring selected from:



B is a ring selected from:



10

wherein A and B cannot simultaneously be a benzene ring;

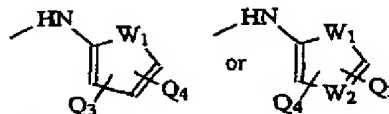
Z is NO<sub>2</sub>, CN, COOH, COR, NHCOR or CONHR;

Y is CF<sub>3</sub>, F, I, Br, Cl, CN CR<sub>3</sub> or SnR<sub>3</sub>;

Q<sub>1</sub> is NCS, SCN, NCO or OCN;

15

Q<sub>2</sub> is a hydrogen, alkyl, halogen, CF<sub>3</sub>, CN CR<sub>3</sub>, SnR<sub>3</sub>, NR<sub>2</sub>, NHCOCH<sub>3</sub>, NHCOCF<sub>3</sub>, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, NHCSCH<sub>3</sub>, NHCSCF<sub>3</sub>, NHCSR, NHSO<sub>2</sub>CH<sub>3</sub>, NHSO<sub>2</sub>R, OR, COR, OCOR, OSO<sub>2</sub>R, SO<sub>2</sub>R, SR,



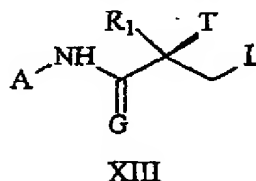
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Q<sub>3</sub> and Q<sub>4</sub> are independently of each other a hydrogen, alkyl, halogen, CF<sub>3</sub>, CN CR<sub>3</sub>, SnR<sub>3</sub>, NR<sub>2</sub>, NHCOCH<sub>3</sub>, NHCOCF<sub>3</sub>, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, NHCSCH<sub>3</sub>, NHCSCF<sub>3</sub>, NHCSR, NHSO<sub>2</sub>CH<sub>3</sub>, NHSO<sub>2</sub>R, OR, COR, OCOR, OSO<sub>2</sub>R, SO<sub>2</sub>R or SR;

$W_1$  is O, NH, NR, NO or S; and

$W_2$  is N or NO;

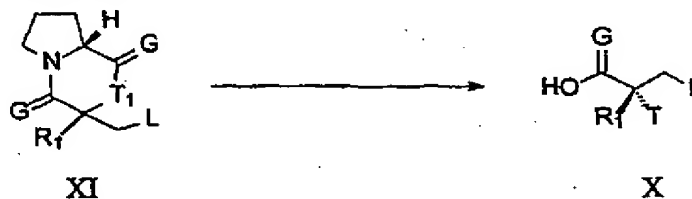
the process comprising the step of coupling a compound of formula XIII:



wherein A, G,  $R_1$  and T are as defined above and L is a leaving group,  
with a compound of formula HX-B wherein B and X are as defined above.

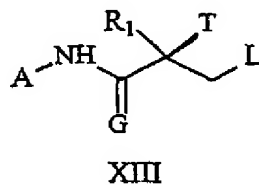
[00052] In one embodiment, the coupling step is carried out in the presence of a base. In another embodiment, the leaving group L is Br. In another embodiment, the compound of formula XIII is prepared by

- i) preparing a compound formula X by ring opening of a cyclic compound of formula XI



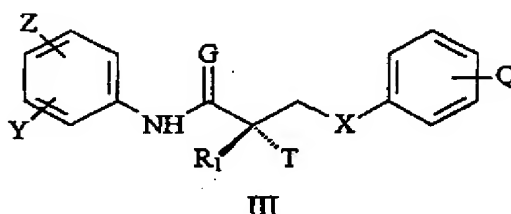
wherein L,  $R_1$ , G and T are as defined above, and  $T_1$  is O or NH; and

- ii) reacting an amine of formula A-NH<sub>2</sub> wherein A is as defined above, with the compound of formula X in the presence of a coupling reagent, to produce the amide of formula XIII.



[00053] In one embodiment, step (a) is carried out in the presence of HBr. In another embodiment, the process further comprises the step of converting the selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

[00054] In another embodiment, the present invention provides process for preparing a selective androgen receptor modulator (SARM) compound represented by the structure of formula III:



wherein

X is O, NH, S, Se, PR or NR;

G is O or S;

T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR

Z is NO<sub>2</sub>, CN, COOH, COR, NHCOR or CONHR;

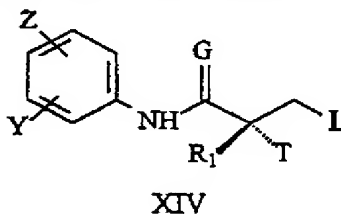
Y is CF<sub>3</sub>, F, I, Br, Cl, CN, CR<sub>3</sub> or SnR<sub>3</sub>;

Q is SCN, NCS, OCN, or NCO;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH; and

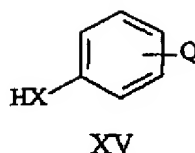
R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;

the process comprising the step of coupling a compound of formula XIV:



wherein Z, Y, G R<sub>1</sub> and T are as defined above and L is a leaving group,

with a compound of formula XV:

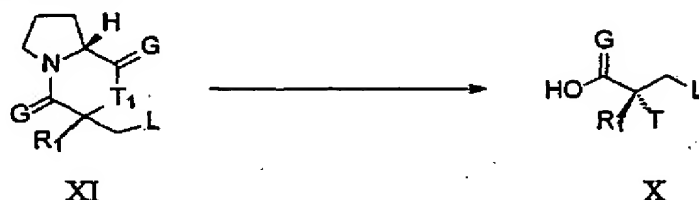


5            wherein Q and X are as defined above.

(00055) In one embodiment, the coupling step is carried out in the presence of a base. In another embodiment, the leaving group L is Br. In another embodiment, the compound

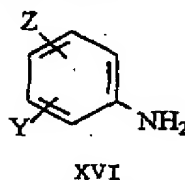
10 of formula XIV is prepared by

- i) preparing a compound formula X by ring opening of a cyclic compound of formula XI:

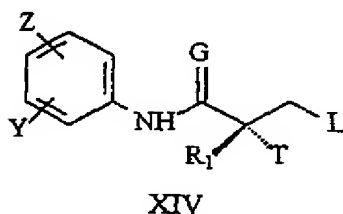


15 wherein L, R<sub>1</sub>, and T are as defined above; G is O and T<sub>1</sub> is O or NH; and

- ii) reacting an amine of formula XVI

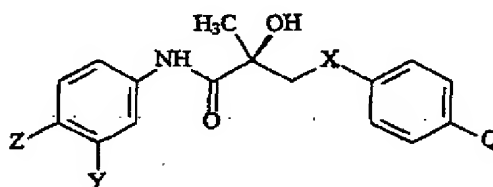


with the compound of formula X in the presence of a coupling reagent, to produce the  
20 compound of formula XIV.



[00056] In one embodiment, step (a) is carried out in the presence of HBr. In another embodiment, the process further comprises the step of converting the selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

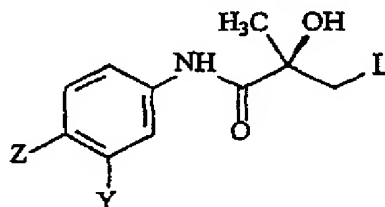
[00057] In another embodiment, the present invention provides process for preparing a selective androgen receptor modulator (SARM) compound represented by the structure of formula IV:



IV

wherein X is O, NH, S, Se, PR, or NR;  
 Z is NO<sub>2</sub>, CN, COOH, COR, NHCOR or CONHR;  
 Y is CF<sub>3</sub>, F, I, Br, Cl, CN, CR<sub>3</sub> or SnR<sub>3</sub>;  
 Q is SCN, NCS, OCN, or NCO; and  
 R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH;

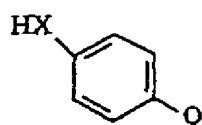
the process comprising the step of coupling an amide of formula XVII:



XVII

wherein Z and Y are as defined above and L is a leaving group,

with a compound of formula XVIII:



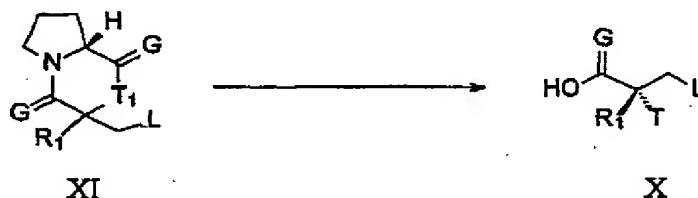
XVIII

wherein Q and X R<sub>2</sub> are as defined above.

5

[00058] In one embodiment, the coupling step is carried out in the presence of a base. In another embodiment, the leaving group L is Br. In another embodiment, the compound of formula XVII is prepared by

- 10 i) preparing a compound formula X by ring opening of a cyclic compound of formula XI

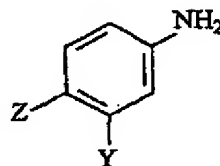


XI

X

wherein L, R<sub>1</sub>, and T are as defined above, G is O and T<sub>1</sub> is O or NH; and

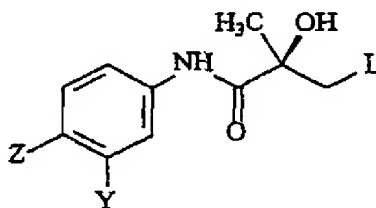
- 15 ii) reacting an amine of formula XXIX



XXIX

with the compound of formula X in the presence of a coupling reagent, to produce the compound of formula XVII.

20



XVII

In one embodiment, step (a) is carried out in the presence of HBr. In another embodiment, the process further comprises the step of purifying the SARM compound using a mixture of ethanol and water. In another embodiment, the process further comprises the step of converting the selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

[00059] The novel selective androgen receptor modulator compounds of the present invention, either alone or as a pharmaceutical composition, are useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with ADAM, such as fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, obesity, sarcopenia, osteopenia, benign prostate hyperplasia, and alterations in mood and cognition; c) treatment of conditions associated with ADIF, such as sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian cancer; d) treatment and/or prevention of acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; g) decreasing the incidence of, halting or causing a regression of prostate cancer; and/or h) inducing apoptosis in a cancer cell.

[00060] The selective androgen receptor modulator compounds of the present invention offer a significant advance over steroidal androgen treatment because the selective androgen receptor modulator compounds of the present invention have been shown in vivo to have an androgenic and anabolic activity of a nonsteroidal ligand for the androgen receptor. Thus, the selective androgen receptor modulator compounds have an androgenic and anabolic activity of a nonsteroidal ligand for the androgen receptor and will not be accompanied by serious side effects, inconvenient modes of administration, or high costs and still have the advantages of oral bioavailability, lack of cross-reactivity with other steroid receptors, and long biological half-lives.

### **BRIEF DESCRIPTION OF THE DRAWINGS**

[00061] The present invention will be understood and appreciated more fully from the following detailed description taken in conjunction with the appended drawings in which:

**Figure 1:** Cytotoxicity of SARM compounds in different cell lines. A) Compound V; B) S-NTBA; C) R-CTF-T-CA-1; and D) R-CTF-T-BA-1.

10

**Figure 2:** Cytotoxicity of SARM compounds in LNCaP prostate cancer cell line (24 hr and 6 day treatment). A) R-CTF-T-BA-1; B) R-CTF-T-CA-1; C) S-NTBA; and D) Compound V.

15 **Figure 3:** Cytotoxicity of SARM compounds in a CV-1 control cell line (24 hr and 4 day treatment). A) R-CTF-T-BA-1; B) R-CTF-T-CA-1; C) S-NTBA; and D) Compound V.

20 **Figure 4:** Cytotoxicity of SARM compounds in PC-3 bone metastatic prostate cancer cell line (24 hr and 4 day treatment). A) R-CTF-T-BA-1; B) R-CTF-T-CA-1; C) S-NTBA; and D) 5-FU.

### **DETAILED DESCRIPTION OF THE INVENTION**

[00062] In one embodiment, this invention provides androgen receptor targeting agents (ARTA). The agents define a new subclass of compounds, which are selective androgen receptor modulators (SARM). The SARM compounds have unexpected antiandrogenic activity of a nonsteroidal ligand for the androgen receptor. In one embodiment, the SARM compounds bind irreversibly to the androgen receptor. In another embodiment, the SARM compounds are androgen receptor antagonists which bind irreversibly to the androgen receptor. In another embodiment, the SARM compounds are alkylating agents. The SARM compounds, either alone or as a composition, are useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example

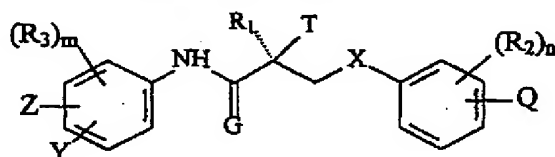
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conditions associated with Androgen Decline in Aging Male (ADAM), such as fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, anemia, obesity, sarcopenia, osteopenia, osteoporosis, benign prostate hyperplasia, alterations in mood and cognition and prostate cancer; c) treatment  
 5 of conditions associated with Androgen Decline in Female (ADIF), such as sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian cancer; d) treatment and/or prevention of acute and/or chronic muscular wasting conditions; e) preventing and/or  
 10 treating dry eye conditions; f) oral androgen replacement therapy; g) decreasing the incidence of, halting or causing a regression of prostate cancer; and/or h) inducing apoptosis in a cancer cell.

[00063] In one embodiment, the present invention provides a selective androgen receptor  
 15 modulator (SARM) compound represented by the structure of formula I:



I

X is a bond, O, CH<sub>2</sub>, NH, S, Se, PR, NO or NR;

G is O or S;

20 T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR;

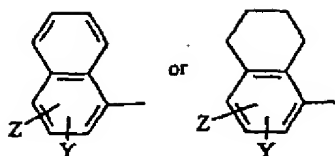
R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH;

R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;

25 R<sub>2</sub> is F, Cl, Br, I, CH<sub>3</sub>, CF<sub>3</sub>, OH, CN, NO<sub>2</sub>, NHCOCH<sub>3</sub>, NHCOCF<sub>3</sub>, NHCOR, alkyl, arylalkyl, OR, NH<sub>2</sub>, NHR, NR<sub>2</sub>, SR;

R<sub>3</sub> is F, Cl, Br, I, CN, NO<sub>2</sub>, COR, COOH, CONHR, CF<sub>3</sub>, SnR<sub>3</sub>, or

R<sub>3</sub> together with the benzene ring to which it is attached forms a fused ring system represented by the structure:



Z is NO<sub>2</sub>, CN, COR, COOH, or CONHR;

Y is CF<sub>3</sub>, F, Br, Cl, I, CN, or SnR<sub>3</sub>;

Q is SCN, NCS, OCN, or NCO;

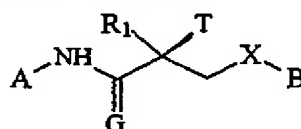
n is an integer of 1-4; and

m is an integer of 1-3.

[00064] In one embodiment, this invention provides an analog of the compound of formula I. In another embodiment, this invention provides a derivative of the compound of formula I. In another embodiment, this invention provides an isomer of the compound of formula I. In another embodiment, this invention provides a metabolite of the compound of formula I. In another embodiment, this invention provides a pharmaceutically acceptable salt of the compound of formula I. In another embodiment, this invention provides a pharmaceutical product of the compound of formula I. In another embodiment, this invention provides a hydrate of the compound of formula I. In another embodiment, this invention provides an N-oxide of the compound of formula I. In another embodiment, this invention provides a combination of any of an analog, derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula I.

[00065] In one embodiment, G in compound I is O. In another embodiment, X in compound I is O. In another embodiment, T in compound I is OH. In another embodiment, R<sub>1</sub> in compound I is CH<sub>3</sub>. In another embodiment, Z in compound I is NO<sub>2</sub>. In another embodiment, Z in compound I is CN. In another embodiment, Y in compound I is CF<sub>3</sub>. In another embodiment, Q in compound I is NCS. In another embodiment, Q in compound I is in the para position. In another embodiment, Z in compound I is in the para position. In another embodiment, Y in compound I is in the meta position. In another embodiment, G in compound I is O, T is OH, R<sub>1</sub> is CH<sub>3</sub>, X is O, Z is NO<sub>2</sub>, Y is CF<sub>3</sub>, and Q is NCS.

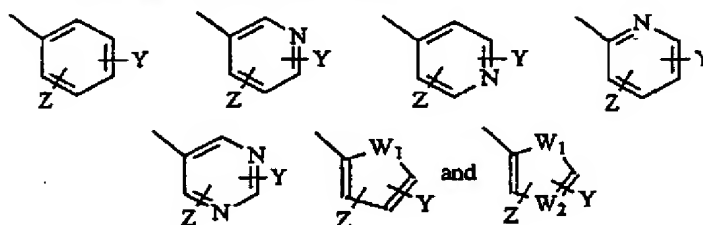
[00066] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula II:



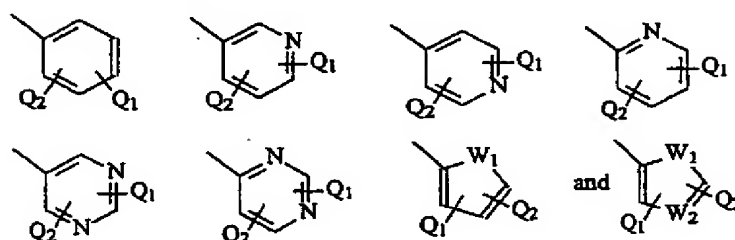
II

- 5            wherein    X is a bond, O, CH<sub>2</sub>, NH, S, Se, PR, NO or NR;  
                          G is O or S;  
                          R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;  
                          T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR;  
                          R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>,  
 10            CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH;

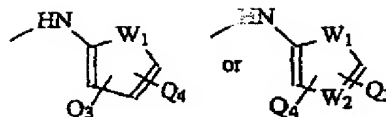
A is a ring selected from:



B is a ring selected from:



- 15            wherein    A and B cannot simultaneously be a benzene ring;  
                          Z is NO<sub>2</sub>, CN, COOH, COR, NHCOR or CONHR;  
                          Y is CF<sub>3</sub>, F, I, Br, Cl, CN CR<sub>3</sub> or SnR<sub>3</sub>;  
                          Q<sub>1</sub> is NCS, SCN, NCO or OCN;  
                          Q<sub>2</sub> is a hydrogen, alkyl, halogen, CF<sub>3</sub>, CN CR<sub>3</sub>, SnR<sub>3</sub>, NR<sub>2</sub>, NHCOCH<sub>3</sub>,  
 20            NHCOCF<sub>3</sub>, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR,  
                          NHCSCH<sub>3</sub>, NHCSCF<sub>3</sub>, NHCSR NHSO<sub>2</sub>CH<sub>3</sub>, NHSO<sub>2</sub>R, OR, COR,  
                          OCOR, OSO<sub>2</sub>R, SO<sub>2</sub>R, SR,



Q<sub>3</sub> and Q<sub>4</sub> are independently of each other a hydrogen, alkyl, halogen, CF<sub>3</sub>, CN, CR<sub>3</sub>, SnR<sub>3</sub>, NR<sub>2</sub>, NHCOCH<sub>3</sub>, NHCOCF<sub>3</sub>, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, NHCSCH<sub>3</sub>, NHCSCH<sub>3</sub>, NHCSR, NHCSO<sub>2</sub>CH<sub>3</sub>, NHCSO<sub>2</sub>R, OR, COR, OCOR, OSO<sub>2</sub>R, SO<sub>2</sub>R or SR;

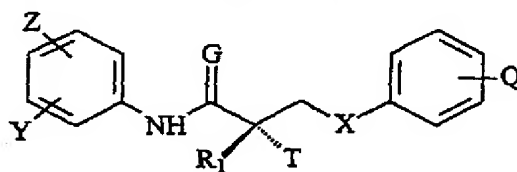
W<sub>1</sub> is O, NH, NR, NO or S; and

W<sub>2</sub> is N or NO.

[00067] In one embodiment, this invention provides an analog of the compound of formula II. In another embodiment, this invention provides a derivative of the compound of formula II. In another embodiment, this invention provides an isomer of the compound of formula II. In another embodiment, this invention provides a metabolite of the compound of formula II. In another embodiment, this invention provides a pharmaceutically acceptable salt of the compound of formula II. In another embodiment, this invention provides a pharmaceutical product of the compound of formula II. In another embodiment, this invention provides a hydrate of the compound of formula II. In another embodiment, this invention provides an N-oxide of the compound of formula II. In another embodiment, this invention provides a combination of any of an analog, derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula II.

[00068] In one embodiment, G in compound II is O. In another embodiment, X in compound II is O. In another embodiment, T in compound II is OH. In another embodiment, R<sub>1</sub> in compound II is CH<sub>3</sub>. In another embodiment, Z in compound II is NO<sub>2</sub>. In another embodiment, Z in compound II is CN. In another embodiment, Y in compound II is CF<sub>3</sub>. In another embodiment, Q<sub>1</sub> in compound II is NCS. In another embodiment, Q<sub>1</sub> in compound II is in the para position. In another embodiment, Z in compound II is in the para position. In another embodiment, Y in compound II is in the meta position. In another embodiment, G in compound II is O, T is OH, R<sub>1</sub> is CH<sub>3</sub>, X is O, Z is NO<sub>2</sub>, Y is CF<sub>3</sub>, and Q<sub>1</sub> is NCS.

[00069] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula III:



### III

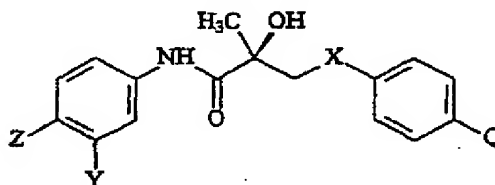
5 wherein X is a bond, O, CH<sub>2</sub>, NH, S, Se, PR, NO or NR;  
G is O or S;  
T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR  
Z is NO<sub>2</sub>, CN, COOH, COR, NHCOR or CONHR;  
Y is CF<sub>3</sub>, F, I, Br, Cl, CN, CR<sub>3</sub> or SnR<sub>3</sub>;  
10 Q is SCN, NCS, OCN, or NCO;  
R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>,  
CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH; and  
R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>.

15 [00070] In one embodiment, this invention provides an analog of the compound of formula III. In another embodiment, this invention provides a derivative of the compound of formula III. In another embodiment, this invention provides an isomer of the compound of formula III. In another embodiment, this invention provides a metabolite of the compound of formula III. In another embodiment, this invention provides a pharmaceutically acceptable salt of the compound of formula III. In another embodiment, this invention provides a pharmaceutical product of the compound of formula III. In another embodiment, this invention provides a hydrate of the compound of formula III. In another embodiment, this invention provides an N-oxide of the compound of formula III. In another embodiment, this invention provides a combination of any of an analog, derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula III.

[00071] In one embodiment, G in compound III is O. In another embodiment, X in  
30 compound III is O. In another embodiment, T in compound III is OH. In another

embodiment,  $R_1$  in compound III is  $CH_3$ . In another embodiment, Z in compound III is  $NO_2$ . In another embodiment, Z in compound III is CN. In another embodiment, Y in compound III is  $CF_3$ . In another embodiment, Q in compound III is NCS. In another embodiment, Q in compound III is in the para position. In another embodiment, Z in compound III is in the para position. In another embodiment, Y in compound III is in the meta position. In another embodiment, G in compound III is O, T is OH,  $R_1$  is  $CH_3$ , X is O, Z is  $NO_2$ , Y is  $CF_3$ , and Q is NCS.

[00072] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula IV:



IV

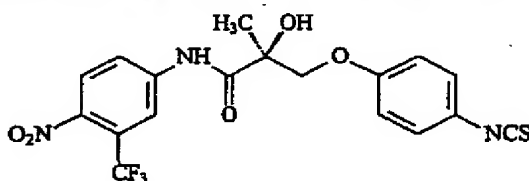
wherein X is a bond, O,  $CH_2$ , NH, S, Se, PR, NO or NR;  
 Z is  $NO_2$ , CN, COOH, COR, NHCOR or CONHR;  
 Y is  $CF_3$ , F, I, Br, Cl, CN,  $CR_3$  or  $SnR_3$ ;  
 Q is SCN, NCS, OCN, or NCO; and  
 R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl,  $CH_2F$ ,  $CHF_2$ ,  $CF_3$ ,  $CF_2CF_3$ , aryl, phenyl, halogen, alkenyl or OH.

[00073] In one embodiment, this invention provides an analog of the compound of formula IV. In another embodiment, this invention provides a derivative of the compound of formula IV. In another embodiment, this invention provides an isomer of the compound of formula IV. In another embodiment, this invention provides a metabolite of the compound of formula IV. In another embodiment, this invention provides a pharmaceutically acceptable salt of the compound of formula IV. In another embodiment, this invention provides a pharmaceutical product of the compound of formula IV. In another embodiment, this invention provides a hydrate of the compound of formula IV. In another embodiment, this invention provides an N-oxide of the compound of formula IV. In another embodiment, this invention provides a combination

of any of an analog, derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula IV.

[00074] In one embodiment, X in compound IV is O. In another embodiment, Z in  
5 compound IV is NO<sub>2</sub>. In another embodiment, Z in compound IV is CN. In another  
embodiment, Y in compound IV is CF<sub>3</sub>. In another embodiment, Q in compound IV is  
NCS.

[00075] In another embodiment, the present invention provides a selective androgen  
10 receptor modulator (SARM) compound represented by the structure of formula V:



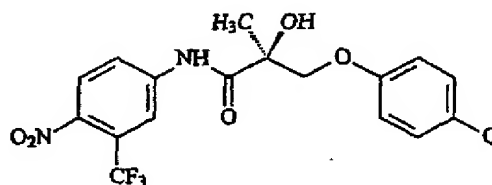
V

[00076] In one embodiment, this invention provides an analog of the compound of  
formula V. In another embodiment, this invention provides a derivative of the compound  
15 of formula V. In another embodiment, this invention provides an isomer of the  
compound of formula V. In another embodiment, this invention provides a metabolite  
of the compound of formula V. In another embodiment, this invention provides a  
pharmaceutically acceptable salt of the compound of formula V. In another embodiment,  
this invention provides a pharmaceutical product of the compound of formula V. In  
20 another embodiment, this invention provides a hydrate of the compound of formula V.  
In another embodiment, this invention provides an N-oxide of the compound of formula  
V. In another embodiment, this invention provides a combination of any of an analog,  
derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product,  
hydrate or N-oxide of the compound of formula V.

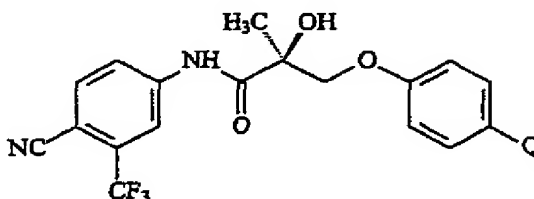
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[00077] As contemplated herein, other specific embodiments of compounds included  
within the scope of the present invention are compounds VI and VII. It is understood  
that included within the scope of the present invention are analogs, derivatives,

metabolites, isomers, pharmaceutically acceptable salts, pharmaceutical products, hydrates, N-oxides or combinations thereof of these compounds:



VI



VII

wherein Q is NCS, SCN, NCO or OCN.

[00078] The substituent R is defined herein as an alkyl, haloalkyl, dihaloalkyl, trihaloalkyl,  $\text{CH}_2\text{F}$ ,  $\text{CHF}_2$ ,  $\text{CF}_3$ ,  $\text{CF}_2\text{CF}_3$ ; aryl, phenyl, halogen, alkenyl, or hydroxyl (OH).

[00079] An "alkyl" group refers to a saturated aliphatic hydrocarbon, including straight-chain, branched-chain and cyclic alkyl groups. In one embodiment, the alkyl group has 1-12 carbons. In another embodiment, the alkyl group has 1-7 carbons. In another embodiment, the alkyl group has 1-6 carbons. In another embodiment, the alkyl group has 1-4 carbons. The alkyl group may be unsubstituted or substituted by one or more groups selected from halogen, hydroxy, alkoxy carbonyl, amido, alkylamido, dialkylamido, nitro, amino, alkylamino, dialkylamino, carboxyl, thio and thioalkyl.

[00080] A "haloalkyl" group refers to an alkyl group as defined above, which is substituted by one or more halogen atoms, e.g. by F, Cl, Br or I.



[00081] An "aryl" group refers to an aromatic group having at least one carbocyclic aromatic group or heterocyclic aromatic group, which may be unsubstituted or substituted by one or more groups selected from halogen, haloalkyl, hydroxy, alkoxy, carbonyl, amido, alkylamido, dialkylamido, nitro, amino, alkylamino, dialkylamino, 5 carboxy or thio or thioalkyl. Nonlimiting examples of aryl rings are phenyl, naphthyl, pyranyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyrazolyl, pyridinyl, furanyl, thiophenyl, thiazolyl, imidazolyl, isoxazolyl, and the like.

[00082] A "hydroxyl" group refers to an OH group. An "alkenyl" group refers to a 10 group having at least one carbon to carbon double bond. A halo group refers to F, Cl, Br or I.

[00083] An "arylalkyl" group refers to an alkyl bound to an aryl, wherein alkyl and aryl are as defined above. An example of an aralkyl group is a benzyl group.

15 [00084] As contemplated herein, the present invention relates to the use of a SARM compound and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide, or combinations thereof. In one embodiment, the invention relates to the use of an analog of the SARM compound. In 20 another embodiment, the invention relates to the use of a derivative of the SARM compound. In another embodiment, the invention relates to the use of an isomer of the SARM compound. In another embodiment, the invention relates to the use of a metabolite of the SARM compound. In another embodiment, the invention relates to the use of a pharmaceutically acceptable salt of the SARM compound. In another 25 embodiment, the invention relates to the use of a pharmaceutical product of the SARM compound. In another embodiment, the invention relates to the use of a hydrate of the SARM compound. In another embodiment, the invention relates to the use of an N-oxide of the SARM compound. In another embodiment, the invention relates to the use of any of a combination of an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, or N-oxide of the SARM compounds 30 of the present invention.

[00085] As defined herein, the term "isomer" includes, but is not limited to, optical isomers and analogs, structural isomers and analogs, conformational isomers and analogs, and the like.

5 [00086] In one embodiment, this invention encompasses the use of various optical isomers of the SARM compound. It will be appreciated by those skilled in the art that the SARMS of the present invention contain at least one chiral center. Accordingly, the SARMS used in the methods of the present invention may exist in, and be isolated in, optically-active or racemic forms. Some compounds may also exhibit polymorphism. It  
10 is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, which form possesses properties useful in the treatment of androgen-related conditions described herein. In one embodiment, the SARMS are the pure (R)-isomers. In another embodiment, the SARMS are the pure (S)-isomers. In another embodiment, the SARMS are a mixture of  
15 the (R) and the (S) isomers. In another embodiment, the SARMS are a racemic mixture comprising an equal amount of the (R) and the (S) isomers. It is well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase).

20

[00087] The invention includes pharmaceutically acceptable salts of amino-substituted compounds with organic and inorganic acids, for example, citric acid and hydrochloric acid. The invention also includes N-oxides of the amino substituents of the compounds described herein. Pharmaceutically acceptable salts can also be prepared from the  
25 phenolic compounds by treatment with inorganic bases, for example, sodium hydroxide. Also, esters of the phenolic compounds can be made with aliphatic and aromatic carboxylic acids, for example, acetic acid and benzoic acid esters.

[00088] This invention further includes derivatives of the SARM compounds. The term  
30 "derivatives" includes but is not limited to ether derivatives, acid derivatives, amide derivatives, ester derivatives and the like. In addition, this invention further includes

hydrates of the SARM compounds. The term "hydrate" includes but is not limited to hemihydrate, monohydrate, dihydrate, trihydrate and the like.

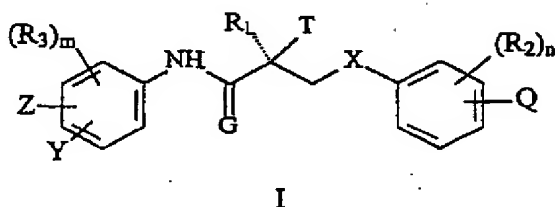
[00089] This invention further includes metabolites of the SARM compounds. The term  
5 "metabolite" means any substance produced from another substance by metabolism or a metabolic process.

[00090] This invention further includes pharmaceutical products of the SARM compounds. The term "pharmaceutical product" means a composition suitable for  
10 pharmaceutical use (pharmaceutical composition), as defined herein.

[00091] In another embodiment, the present invention provides process for preparing the selective androgen receptor modulator (SARM) compounds of the present invention.

[00092] The process of the present invention is suitable for large-scale preparation, since all of the steps give rise to highly pure compounds, thus avoiding complicated purification procedures which ultimately lower the yield. Thus the present invention provides methods for the synthesis of non-steroidal agonist compounds, that can be used for industrial large-scale synthesis, and that provide highly pure products in high yield.  
20

[00093] In one embodiment, the present invention provides process for preparing the selective androgen receptor modulator (SARM) compound represented by the structure of formula I:



wherein X is a O, NH, S, Se, PR, or NR;

G is O or S;

T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR;

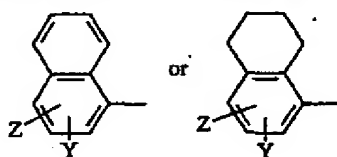
R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>,  
CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH;

R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;

R<sub>2</sub> is F, Cl, Br, I, CH<sub>3</sub>, CF<sub>3</sub>, OH, CN, NO<sub>2</sub>, NHCOCH<sub>3</sub>,  
NHCOCF<sub>3</sub>, NHCOR, alkyl, arylalkyl, OR, NH<sub>2</sub>, NHR, NR<sub>2</sub>, SR;

R<sub>3</sub> is F, Cl, Br, I, CN, NO<sub>2</sub>, COR, COOH, CONHR, CF<sub>3</sub>, SnR<sub>3</sub>, or

R<sub>3</sub> together with the benzene ring to which it is attached forms a fused  
ring system represented by the structure:



Z is NO<sub>2</sub>, CN, COR, COOH, or CONHR;

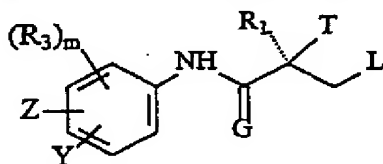
Y is CF<sub>3</sub>, F, Br, Cl, I, CN, or SnR<sub>3</sub>;

Q is SCN, NCS, OCN, or NCO;

n is an integer of 1-4; and

m is an integer of 1-3;

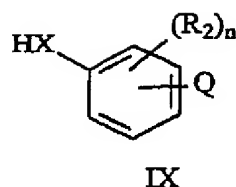
the process comprising the step of coupling a compound of formula VIII:



VIII

wherein Z, Y, G, R<sub>1</sub>, T, R<sub>3</sub> and m are as defined above and L is a leaving group,

with a compound of formula IX:



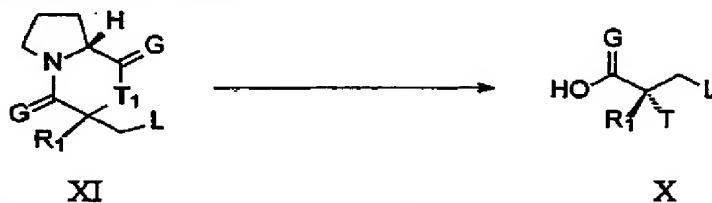
wherein Q, X, R<sub>2</sub> and n are as defined above.

5

[00094] In one embodiment, the coupling step is carried out in the presence of a base. In another embodiment, the leaving group L is Br. In another embodiment, the compound of formula VIII is prepared by

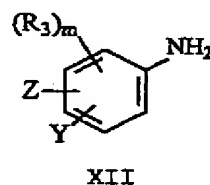
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- i) preparing a compound of formula X by ring opening of a cyclic compound of formula XI



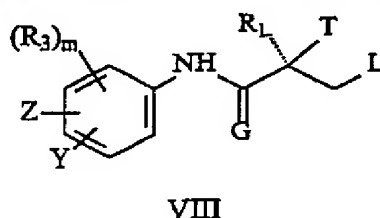
wherein L, R<sub>1</sub>, G and T are as defined above, and T<sub>1</sub> is O or NH; and

- ii) reacting an amine of formula XII:



15

wherein Z, Y, R<sub>3</sub> and m are as defined above, with the compound of formula X, in the presence of a coupling reagent, to produce the compound of formula VIII.

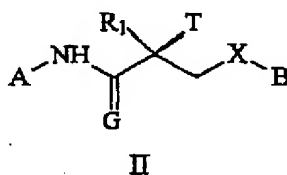


20

[00095] In one embodiment, step (a) is carried out in the presence of HBr. In another embodiment, the process further comprises the step of converting the selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative,

pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

[00096] In another embodiment, the present invention provides process for preparing a selective androgen receptor modulator (SARM) compound represented by the structure of formula II:



wherein X is O, NH, S, Se, PR, or NR;

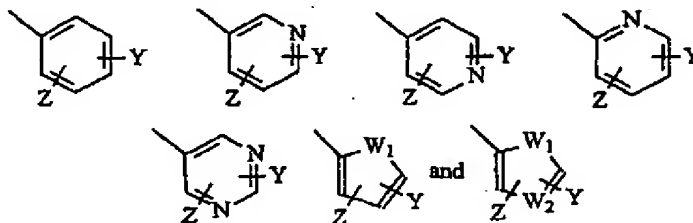
G is O or S;

R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;

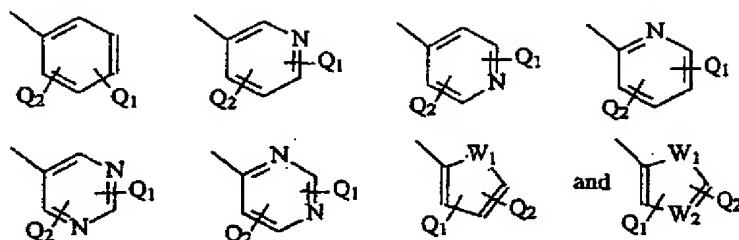
T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH;

A is a ring selected from:



B is a ring selected from:



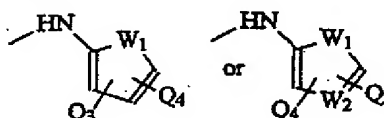
wherein A and B cannot simultaneously be a benzene ring;

Z is NO<sub>2</sub>, CN, COOH, COR, NHCOR or CONHR;

Y is CF<sub>3</sub>, F, I, Br, Cl, CN CR<sub>3</sub> or SnR<sub>3</sub>;

5 Q<sub>1</sub> is NCS, SCN, NCO or OCN;

Q<sub>2</sub> is a hydrogen, alkyl, halogen, CF<sub>3</sub>, CN CR<sub>3</sub>, SnR<sub>3</sub>, NR<sub>2</sub>, NHCOCH<sub>3</sub>,  
 NHCOCF<sub>3</sub>, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR,  
 NHCSCH<sub>3</sub>, NHCSCF<sub>3</sub>, NHCSR NHSO<sub>2</sub>CH<sub>3</sub>, NHSO<sub>2</sub>R, OR, COR,  
 OCOR, OSO<sub>2</sub>R, SO<sub>2</sub>R, SR,



10

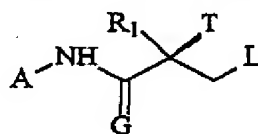
Q<sub>3</sub> and Q<sub>4</sub> are independently of each other a hydrogen, alkyl,  
 halogen, CF<sub>3</sub>, CN CR<sub>3</sub>, SnR<sub>3</sub>, NR<sub>2</sub>, NHCOCH<sub>3</sub>, NHCOCF<sub>3</sub>, NHCOR,  
 NHCONHR, NHCOOR, OCONHR, CONHR, NHCSCH<sub>3</sub>, NHCSCF<sub>3</sub>,  
 NHCSR NHSO<sub>2</sub>CH<sub>3</sub>, NHSO<sub>2</sub>R, OR, COR, OCOR, OSO<sub>2</sub>R, SO<sub>2</sub>R or SR;

15

W<sub>1</sub> is O, NH, NR, NO or S; and

W<sub>2</sub> is N or NO;

the process comprising the step of coupling a compound of formula XIII:



XIII

20

wherein A, G, R<sub>1</sub> and T are as defined above and L is a leaving group,  
 with a compound of formula HX-B wherein B and X are as defined above.

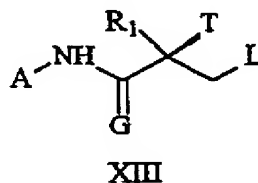
[00097] In one embodiment, the coupling step is carried out in the presence of a base. In another embodiment, the leaving group L is Br. In another embodiment, the compound of formula XIII is prepared by

- 5           i)     preparing a compound formula X by ring opening of a cyclic compound of formula XI



wherein L, R<sub>1</sub>, G and T are as defined above, and T<sub>1</sub> is O or NH; and

- 10           ii)    reacting an amine of formula A-NH<sub>2</sub> wherein A is as defined above, with the compound of formula X in the presence of a coupling reagent, to produce the amide of formula XIII.



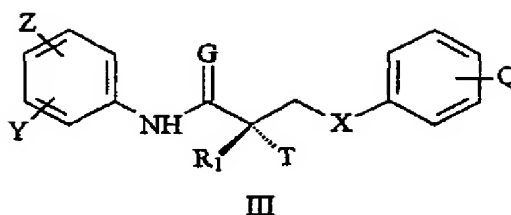
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[00098] In one embodiment, step (a) is carried out in the presence of HBr. In another embodiment, the process further comprises the step of converting the selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

[00099] In another embodiment, the present invention provides process for preparing a selective androgen receptor modulator (SARM) compound represented by the structure of formula III:

25





wherein X is O, NH, S, Se, PR or NR;

G is O or S;

T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR

Z is NO<sub>2</sub>, CN, COOH, COR, NHCOR or CONHR;

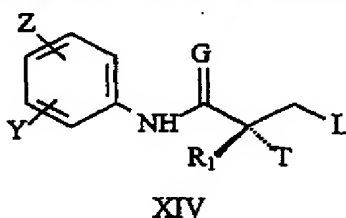
Y is CF<sub>3</sub>, F, I, Br, Cl, CN, CR<sub>3</sub> or SnR<sub>3</sub>;

Q is SCN, NCS, OCN, or NCO;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH; and

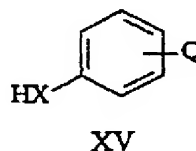
R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;

the process comprising the step of coupling a compound of formula XIV:



wherein Z, Y, G R<sub>1</sub> and T are as defined above and L is a leaving group,

with a compound of formula XV:



wherein Q and X are as defined above.

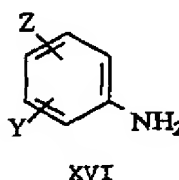
[000100] In one embodiment, the coupling step is carried out in the presence of a base. In another embodiment, the leaving group L is Br. In another embodiment, the compound of formula XIV is prepared by

- 5 i) preparing a compound formula X by ring opening of a cyclic compound of formula XI



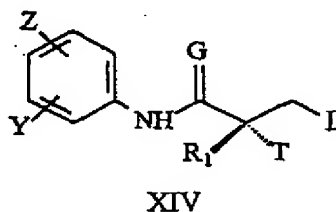
wherein L, R<sub>1</sub>, and T are as defined above, G is O and T<sub>1</sub> is O or NH; and

- 10 ii) reacting an amine of formula XVI



with the compound of formula X in the presence of a coupling reagent, to produce the compound of formula XIV.

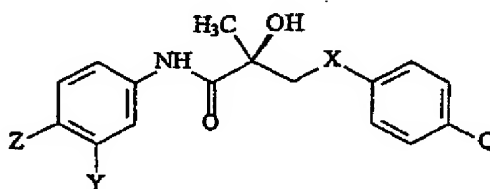
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- 20 [000101] In one embodiment, step (a) is carried out in the presence of HBr. In another embodiment, the process further comprises the step of converting the selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

25

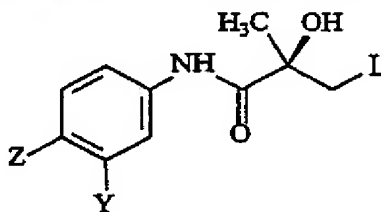
[000102] In another embodiment, the present invention provides process for preparing a selective androgen receptor modulator (SARM) compound represented by the structure of formula IV:



IV

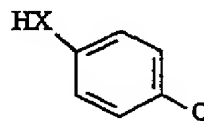
wherein X is O, NH, S, Se, PR, or NR;  
 Z is NO<sub>2</sub>, CN, COOH, COR, NHCOR or CONHR;  
 Y is CF<sub>3</sub>, F, I, Br, Cl, CN, CR<sub>3</sub> or SnR<sub>3</sub>;  
 Q is SCN, NCS, OCN, or NCO; and  
 R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>,  
 CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH;

the process comprising the step of coupling an amide of formula XVII:



XVII

wherein Z and Y are as defined above and L is a leaving group,  
 with a compound of formula XVIII



XVIII

wherein Q and X R<sub>2</sub> are as defined above.

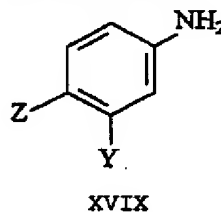
[000103] In one embodiment, the coupling step is carried out in the presence of a base. In another embodiment, the leaving group L is Br. In another embodiment, the compound of formula XVII is prepared by

- 5 i) preparing a compound formula X by ring opening of a cyclic compound of formula XI

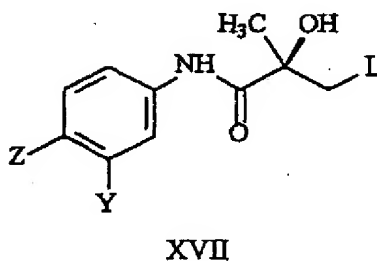


wherein L, R<sub>1</sub>, and T are as defined above, G is O and T<sub>1</sub> is O or NH; and

- 10 ii) reacting an amine of formula XIX



with the compound of formula X in the presence of a coupling reagent, to produce the compound of formula XVII.



- [000104] In one embodiment, step (a) is carried out in the presence of HBr. In another embodiment, the process further comprises the step of converting the selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.
- 20

[000105] As demonstrated herein, Applicants have found that when the purification step of the SARM compounds is carried out in the presence of a nontoxic organic solvent and water, such as ethanol and water, for example by recrystallization from a mixture of ethanol and water, a highly pure product with excellent crystal stability is obtained in high yields. In addition, the use of a nontoxic organic solvent/water for purification is safe and cheap, and avoids any biological hazards that may arise from the use of toxic organic solvents such as hexane. In one embodiment, the nontoxic organic solvent is ethanol.

10 [000106] Thus, in one embodiment, the present invention provides a synthetic process for preparing the SARM compounds described herein, which involves a purification step comprising crystallization of the SARM product using a mixture of a nontoxic organic solvent and water. In one embodiment, the nontoxic organic solvent is ethanol. In a particular embodiment, the crystallization step comprises mixing an ethanol solution comprising the SARM compound with water, so as to crystallize the SARM compound. In a further embodiment, the process further comprises the step of collecting the SARM compound by filtration.

[000107] The process of the present invention is suitable for large-scale preparation, since all of the steps give rise to highly pure compounds, thus avoiding complicated purification procedures which ultimately lower the yield. Thus the present invention provides methods for the synthesis of non-steroidal agonist compounds, that can be used for industrial large-scale synthesis, and that provide highly pure products in high yield. In addition, the methods described by the present invention utilize safe, environmentally friendly and cheap reagents and purification steps, thus avoiding any undesirable toxicological issues that may arise from the use of toxic, environmentally unfriendly or biologically unstable reagents.

[000108] It should be apparent to a person skilled in the art that any nontoxic organic solvent is suitable in the methods of the present invention, for example alcohols such as methanol or ethanol, aromatic compounds such as toluene and xylene, DMSO, THF, cyclohexane and the like.

[000109] In one embodiment, the nontoxic organic solvent is ethanol. Any grade and purity level of ethanol is suitable. In one embodiment, the ethanol is neat ethanol. In another embodiment, the ethanol is an ethanol solution that contains denaturants, such as toluene, methanol and the like.

5

[000110] It is understood to a person skilled in the art that when  $T_1$  is O or NH, T is compound VIII is O or  $NH_2$ . Thus, when T in compound I is OR, the reaction will involve a further step of converting the OH to OR by a reaction with, for example, an alkyl halide R-X. When T in compound I is  $NHCOR$ ,  $NHCOCH_3$ , the reaction will  
10 involve a further step of converting the  $NH_2$  to  $NHCOR$  or  $NHCOCH_3$ , by a reaction with, for example, the corresponding acyl chloride  $ClCOR$  or  $ClCOCH_3$ .

[000111] In one embodiment, the coupling step defined hereinabove is carried out in the presence of a base. Any suitable base that will deprotonate the hydrogen of the -  
15  $XH$  moiety (for example, a phenol moiety when X is O) and allow the coupling may be used. Nonlimiting examples of bases are carbonates such as alkali carbonates, for example sodium carbonate ( $Na_2CO_3$ ), potassium carbonate ( $K_2CO_3$ ) and cesium carbonate ( $Cs_2CO_3$ ); bicarbonates such as alkali metal bicarbonates, for example sodium bicarbonate ( $NaHCO_3$ ), potassium bicarbonate ( $KHCO_3$ ), alkali metal hydrides such as  
20 sodium hydride (NaH), potassium hydride (KH) and lithium hydride (LiH), and the like.

[000112] The leaving group L is defined herein as any removable group customarily considered for chemical reactions, as will be known to the person skilled in the art. Suitable leaving groups are halogens, for example F, Cl, Br and I; alkyl  
25 sulfonate esters ( $-OSO_2R$ ) wherein R is an alkyl group, for example methanesulfonate (mesylate), trifluoromethanesulfonate, ethanesulfonate, 2,2,2-trifluoroethanesulfonate, perfluoro butanesulfonate; aryl sulfonate esters ( $-OSO_2Ar$ ) wherein Ar is an aryl group, for example p-toluoysulfonate (tosylate), benzenesulphonate which may be unsubstituted or substituted by methyl, chlorine, bromine, nitro and the like;  $NO_3$ ,  $NO_2$ ,  
30 or sulfate, sulfite, phosphate, phosphite, carboxylate, imino ester,  $N_2$  or carbamate.

[000113] The reaction is conveniently carried out in a suitable inert solvent or diluent such as, for example, tetrahydrofuran, diethyl ether, aromatic amines such as pyridine; aliphatic and aromatic hydrocarbons such as benzene, toluene, and xylene; dimethylsulfoxide (DMSO), dimethylformamide (DMF), and dimethylacetamide (DMAC). The reaction is suitably carried out at a temperature in the range, for example, -20 to 120 C., for example at or near ambient temperature.

[000114] The coupling reagent defined hereinabove is a reagent capable of turning the carboxylic acid/ thiocarboxylic acid of formula X into a reactive derivative thereof, thus enabling coupling with the respective amine to form an amide/thioamide bond. A suitable reactive derivative of a carboxylic acid / thiocarboxylic acid is, for example, an acyl halide / thioacyl halide, for example an acyl / thioacyl chloride formed by the reaction of the acid / thioacid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester/thioester, for example an ester/thioester formed by the reaction of the acid/thioacid and a phenol, an ester/thioester or an alcohol such as methanol, ethanol, isopropanol, butanol or N-hydroxybenzotriazole; an acyl/thioacyl azide, for example an azide formed by the reaction of the acid/thioacid and azide such as diphenylphosphoryl azide; an acyl cyanide/thioacyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid/thioacid and a carbodiimide such as dicyclohexylcarbodiimide.

[000115] The reaction is conveniently carried out in a suitable inert solvent or diluent as described hereinabove, suitably in the presence of a base such as triethylamine, and at a temperature in the range, as described above.

#### **Biological Activity of Selective Androgen Modulator Compounds**

[000116] The SARM compounds provided herein are compounds, which are selective androgen receptor modulators (SARM), which have an unexpected antiandrogenic activity of a nonsteroidal ligand for the androgen receptor. Furthermore,

several of the SARM compounds bind irreversibly to the androgen receptor. Moreover, several of the SARM compounds of the present invention are alkylating agents.

[000117] As contemplated herein, the appropriately substituted SARM compounds  
5 of the present invention are useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with Androgen Decline in Aging Male (ADAM), such as fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, anemia, obesity, sarcopenia, osteopenia, osteoporosis, benign prostate hyperplasia, alterations in  
10 mood and cognition and prostate cancer; c) treatment of conditions associated with ADIF, such as sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian cancer; d) treatment and/or prevention of acute and/or chronic muscular wasting conditions; e)  
15 preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; g) decreasing the incidence of, halting or causing a regression of prostate cancer; and/or h) inducing apoptosis in a cancer cell.

[000118] As used herein, receptors for extracellular signaling molecules are  
20 collectively referred to as "cell signaling receptors". Many cell signaling receptors are transmembrane proteins on a cell surface; when they bind an extracellular signaling molecule (i.e., a ligand), they become activated so as to generate a cascade of intracellular signals that alter the behavior of the cell. In contrast, in some cases, the receptors are inside the cell and the signaling ligand has to enter the cell to activate  
25 them; these signaling molecules therefore must be sufficiently small and hydrophobic to diffuse across the plasma membrane of the cell.

[000119] Steroid hormones are one example of small hydrophobic molecules that  
diffuse directly across the plasma membrane of target cells and bind to intracellular cell  
30 signaling receptors. These receptors are structurally related and constitute the intracellular receptor superfamily (or steroid-hormone receptor superfamily). Steroid hormone receptors include progesterone receptors, estrogen receptors, androgen



receptors, glucocorticoid receptors, and mineralocorticoid receptors. In one embodiment, the present invention is directed to androgen receptors.

[000120] In addition to ligand binding to the receptors, the receptors can be  
5 blocked to prevent ligand binding. When a substance binds to a receptor, the three-  
dimensional structure of the substance fits into a space created by the three- dimensional  
structure of the receptor in a ball and socket configuration. The better the ball fits into  
the socket, the more tightly it is held. This phenomenon is called affinity. If the affinity  
of a substance is greater than the original hormone, it will compete with the hormone  
10 and bind the binding site more frequently. Once bound, signals may be sent through the  
receptor into the cells, causing the cell to respond in some fashion. This is called  
activation. On activation, the activated receptor then directly regulates the transcription  
of specific genes. But the substance and the receptor may have certain attributes, other  
than affinity, in order to activate the cell. Chemical bonds between atoms of the  
15 substance and the atoms of the receptors may form. In some cases, this leads to a change  
in the configuration of the receptor, which is enough to begin the activation process  
(called signal transduction).

[000121] In another embodiment, the present invention is directed to selective  
20 androgen receptor modulator compounds, which are antagonist compounds. A receptor  
agonist is a substance, which binds receptors and activates them. A receptor antagonist  
is a substance which binds receptors and inactivates them. Thus, in one embodiment,  
the SARM compounds of the present invention are useful in binding to and inactivating  
steroidal hormone receptors. In one embodiment, the antagonist compound of the  
25 present invention is an antagonist which binds the androgen receptor. In another  
embodiment, the compound has high affinity for the androgen receptor.

[000122] Assays to determine whether the compounds of the present invention are  
AR agonists or antagonists are well known to a person skilled in the art. For example,  
30 AR agonistic activity can be determined by monitoring the ability of the SARM  
compounds to maintain and/or stimulate the growth of AR containing tissue such as  
prostate and seminal vesicles, as measured by weight. AR antagonistic activity can be

determined by monitoring the ability of the SARM compounds inhibit the growth of AR containing tissue.

[000123] An androgen receptor is an androgen receptor of any species, for example  
5 a mammal. In one embodiment, the androgen receptor is an androgen receptor of a human.

[000124] The compounds of the present invention bind either reversibly or  
irreversibly to an androgen receptor. In one embodiment, the SARM compounds bind  
10 reversibly to an androgen receptor. In another embodiment, the SARM compounds bind  
reversibly to an androgen receptor of a mammal. In another embodiment, the SARM  
compounds bind reversibly to an androgen receptor of a human. Reversible binding of a  
compound to a receptor means that a compound can detach from the receptor after  
binding.

15 [000125] In another embodiment, the SARM compounds bind irreversibly to an  
androgen receptor. In one embodiment, the SARM compounds bind irreversibly to an  
androgen receptor of a mammal. In another embodiment, the SARM compounds bind  
irreversibly to an androgen receptor of a human. Thus, in one embodiment, the  
20 compounds of the present invention may contain a functional group (e.g. affinity label)  
that allows alkylation of the androgen receptor (i.e. covalent bond formation). Thus, in  
this case, the compounds are alkylating agents which bind irreversibly to the receptor  
and, accordingly, cannot be displaced by a steroid, such as the endogenous ligands DHT  
and testosterone. An "alkylating agent" is defined herein as an agent which alkylates  
25 (forms a covalent bond) with a cellular component, such as DNA, RNA or enzyme. It is  
a highly reactive chemical that introduces alkyl radicals into biologically active  
molecules and thereby prevents their proper functioning. The alkylating moiety is an  
electrophilic group that interacts with nucleophilic moieties in cellular components. For  
example, in one embodiment, an alkylating group is an isocyanate moiety, an  
30 electrophilic group which forms covalent bonds with nucleophilic groups (N, O, S etc.)  
in cellular components. In another embodiment, an alkylating group is an isothiocyanate  
moiety, another electrophilic group which forms covalent bonds with nucleophilic

groups (N, O, S etc.) in cellular components. In another embodiment, an alkylating group is a haloalkyl ( $\text{CH}_2\text{X}$  wherein X is halogen), an electrophilic group which forms covalent bonds with nucleophilic groups in cellular components. In another embodiment, an alkylating group is a haloalkyl-amido ( $\text{NHCOCH}_2\text{X}$  wherein X is halogen), an electrophilic group which forms covalent bonds with nucleophilic groups in cellular components.

[000126] In one embodiment, the SARM compounds of the present invention are androgen receptor antagonists which bind irreversibly to the androgen receptor of a mammal, for e.g. a human. In one embodiment, the compounds are alkylating agents.

[000127] Thus, in one embodiment, the present invention further provides a method of binding a selective androgen receptor modulator compound to an androgen receptor, comprising the step of contacting the androgen receptor with the selective androgen receptor modulator compound of the present invention, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to bind the selective androgen receptor modulator compound to the androgen receptor.

[000128] In another embodiment, the present invention further provides a method of irreversibly binding a selective androgen receptor modulator compound to an androgen receptor, comprising the step of contacting the androgen receptor with the selective androgen receptor modulator compound of the present invention, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to irreversibly bind the selective androgen receptor modulator compound to the androgen receptor.

[000129] In another embodiment, the present invention further provides a method of alkylating an androgen receptor, comprising the step of contacting the androgen receptor with the selective androgen receptor modulator compound of the present invention, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable

salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to alkylate the androgen receptor.

5 [000130] In another embodiment, the present invention provides a method of suppressing spermatogenesis in a subject, comprising the step of contacting an androgen receptor of the subject the selective androgen receptor modulator compound of the present invention, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to suppress sperm production.

10

[000131] In another embodiment, the present invention provides a method of contraception in a male subject, comprising the step of administering to the subject the selective androgen receptor modulator compound of the present invention, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to suppress sperm production in the subject, thereby effecting contraception in the subject.

20 [000132] In another embodiment, the present invention further provides a method of hormone therapy, comprising the step of contacting an androgen receptor of a subject with the selective androgen receptor modulator compound of the present invention, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to bind the selective androgen receptor modulator compound to the androgen receptor and effect a change in an androgen-dependent condition.

25

[000133] In another embodiment, the present invention provides a method of hormone replacement therapy comprising the step of contacting an androgen receptor of a subject with the selective androgen receptor modulator compound of the present invention, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to effect a change in an androgen-dependent condition.

30

[000134] In another embodiment, the present invention further provides a method of treating a subject having a hormone related condition, comprising the step of administering to the subject the selective androgen receptor modulator compound of the present invention, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to bind the selective androgen receptor modulator compound to the androgen receptor and effect a change in an androgen-dependent condition.

[000135] Androgen- dependent conditions which may be treated according to the present invention include those conditions which are associated with aging, such as hypogonadism, sarcopenia, erythropoiesis, osteoporosis, and any other conditions later determined to be dependent upon low androgen (e.g., testosterone) levels.

[000136] In another embodiment, the present invention further provides a method of treating a subject suffering from prostate cancer, comprising the step of administering to the subject the selective androgen receptor modulator compound of the present invention, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to treat prostate cancer in the subject.

20

[000137] In another embodiment, the present invention provides a method of preventing prostate cancer in a subject, comprising the step of administering to the subject the selective androgen receptor modulator compound of the present invention, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to prevent prostate cancer in the subject.

[000138] In another embodiment, the present invention further provides a method of delaying the progression of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to the subject selective androgen receptor modulator compound of the present invention, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide

or any combination thereof, in an amount effective to delay the progression of prostate cancer in the subject.

[000139] In another embodiment, the present invention further provides a method  
5 of preventing the recurrence of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to the subject the selective androgen receptor modulator compound of the present invention, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to prevent the recurrence of  
10 prostate cancer in the subject.

[000140] In another embodiment, the present invention provides a method of treating the recurrence of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to the subject the selective androgen receptor  
15 modulator compound of the present invention, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to treat the recurrence of prostate cancer in the subject.

[000141] Furthermore, stimulation of the Androgen Receptor stimulates the production of tears, and thus the SARM compounds of the present invention may be used to treat dry eye conditions. Therefore, according to another embodiment of the present invention, a method is provided for treating a dry eye condition in a subject suffering from dry eyes, comprising the step of administering to said subject the  
25 selective androgen receptor modulator compound of formulas I-V and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to treat dry eyes in the subject.

[000142] According to another embodiment of the present invention, a method is provided for preventing a dry eye condition in a subject, comprising the step of administering to said subject the selective androgen receptor modulator compound of

formulas I-V and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to prevent dry eyes in the subject.

5

[000143] In another embodiment, the present invention provides a method of inducing apoptosis in a prostate cancer cell, comprising the step of contacting the cell with the selective androgen receptor modulator compound of the present invention, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to induce apoptosis in the cancer cell.

[000144] As defined herein, "apoptosis", or programmed cell death, is a form of cell death in which a programmed sequence of events leads to the elimination of cells without releasing harmful substances into the surrounding area. Apoptosis plays a crucial role in developing and maintaining health by eliminating old cells, unnecessary cells, and unhealthy cells.

[000145] As defined herein, "contacting" means that the SARM compound of the present invention is introduced into a sample containing the enzyme in a test tube, flask, tissue culture, chip, array, plate, microplate, capillary, or the like, and incubated at a temperature and time sufficient to permit binding of the SARM to the enzyme. Methods for contacting the samples with the SARM or other specific binding components are known to those skilled in the art and may be selected depending on the type of assay protocol to be run. Incubation methods are also standard and are known to those skilled in the art.

[000146] In another embodiment, the term "contacting" means that the SARM compound of the present invention is introduced into a subject receiving treatment, and the SARM compound is allowed to come in contact with the androgen receptor *in vivo*.

[000147] As used herein, the term "treating" includes preventative as well as disorder remitative treatment. As used herein, the terms "reducing", "suppressing" and "inhibiting" have their commonly understood meaning of lessening or decreasing. As used herein, the term "progression" means increasing in scope or severity, advancing,  
5 growing or becoming worse. As used herein, the term "recurrence" means the return of a disease after a remission. As used herein, the term "delaying" means stopping, *hindering, slowing down, postponing, holding up or setting back*.

[000148] As used herin, the term "administering" refers to bringing a subject in  
10 contact with a SARM compound of the present invention. As used herein, administration can be accomplished *in vitro*, i.e. in a test tube, or *in vivo*, i.e. in cells or tissues of living organisms, for example humans. In one embodiment, the present invention encompasses administering the compounds of the present invention to a subject.

15 [000149] The term "libido, as used herein, means sexual desire.

[000150] The term "erectile", as used herein, means capable of being erected. An  
erectile tissue is a tissue, which is capable of being greatly dilated and made rigid by the distension of the numerous blood vessels which it contains.

20 [000151] "Hypogonadism" is a condition resulting from or characterised by abnormally decreased functional activity of the gonads, with retardation of growth and sexual development. "Osteopenia" refers to decreased calcification or density of bone. This is a term which encompasses all skeletal systems in which such a condition is  
25 noted.

[000152] "Osteoporosis" refers to a thinning of the bones with reduction in bone  
mass due to depletion of calcium and bone protein. Osteoporosis predisposes a person to fractures, which are often slow to heal and heal poorly. Unchecked osteoporosis can  
30 lead to changes in posture, physical abnormality, and decreased mobility.



[000153] "BPH (benign prostate hyperplasia)" is a nonmalignant enlargement of the prostate gland, and is the most common non-malignant proliferative abnormality found in any internal organ and the major cause of morbidity in the adult male. BPH occurs in over 75% of men over 50 years of age, reaching 88% prevalence by the ninth decade. BPH frequently results in a gradual squeezing of the portion of the urethra which traverses the prostate (prostatic urethra). This causes patients to experience a frequent urge to urinate because of incomplete emptying of the bladder and urgency of urination. The obstruction of urinary flow can also lead to a general lack of control over urination, including difficulty initiating urination when desired, as well as difficulty in preventing urinary flow because of the inability to empty urine from the bladder, a condition known as overflow urinary incontinence, which can lead to urinary obstruction and to urinary failure.

[000154] "Cognition" refers to the process of knowing, specifically the process of being aware, knowing, thinking, learning and judging. Cognition is related to the fields of psychology, linguistics, computer science, neuroscience, mathematics, ethology and philosophy. The term "mood" refers to a temper or state of the mind. As contemplated herein, alterations means any change for the positive or negative, in cognition and/or mood.

20

[000155] The term "depression" refers to an illness that involves the body, mood and thoughts, that affects the way a person eats, sleeps and the way one feels about oneself, and thinks about things. The signs and symptoms of depression include loss of interest in activities, loss of appetite or overeating, loss of emotional expression, an empty mood, feelings of hopelessness, pessimism, guilt or helplessness, social withdrawal, fatigue, sleep disturbances, trouble concentrating, remembering, or making decisions, restlessness, irritability, headaches, digestive disorders or chronic pain.

[000156] The term "hair loss", medically known as alopecia, refers to baldness as in the very common type of male-pattern baldness. Baldness typically begins with patch hair loss on the scalp and sometimes progresses to complete baldness and even loss of body hair. Hair loss affects both males and females.

[000157] "Anemia" refers to the condition of having less than the normal number of red blood cells or less than the normal quantity of hemoglobin in the blood. The oxygen-carrying capacity of the blood is, therefore, decreased. Persons with anemia  
5 may feel tired and fatigue easily, appear pale, develop palpitations and become usually short of breath. Anemia is caused by four basic factors: a) hemorrhage (bleeding); b) hemolysis (excessive destruction of red blood cells); c) underproduction of red blood cells; and d) not enough normal hemoglobin. There are many forms of anemia, including aplastic anemia, benzene poisoning, Fanconi anemia, hemolytic disease of the  
10 newborn, hereditary spherocytosis, iron deficiency anemia, osteopetrosis, pernicious anemia, sickle cell disease, thalassemia, myelodysplastic syndrome, and a variety of bone marrow diseases. As contemplated herein, the SARM compounds of the present invention are useful in preventing and/or treating any one or more of the above-listed forms of anemia.

15

[000158] "Obesity" refers to the state of being well above one's normal weight. Traditionally, a person is considered to be obese if they are more than 20 percent over their ideal weight. Obesity has been more precisely defined by the National Institute of Health (NIH) as a Body to Mass Index (BMI) of 30 or above. Obesity is often  
20 multifactorial, based on both genetic and behavioral factors. Overweight due to obesity is a significant contributor to health problems. It increases the risk of developing a number of diseases including: Type 2 (adult-onset) diabetes; high blood pressure (hypertension); stroke (cerebrovascular accident or CVA); heart attack (myocardial infarction or MI); heart failure (congestive heart failure); cancer (certain forms such as  
25 cancer of the prostate and cancer of the colon and rectum); gallstones and gallbladder disease (cholecystitis); Gout and gouty arthritis; osteoarthritis (degenerative arthritis) of the knees, hips, and the lower back; sleep apnea (failure to breath normally during sleep, lowering blood oxygen); and Pickwickian syndrome (obesity, red face, underventilation and drowsiness). As contemplated herein, the term "obesity" includes any one of the  
30 above-listed obesity-related conditions and diseases. Thus the SARM compounds of the present invention are useful in preventing and/or treating obesity and any one or more of the above-listed obesity-related conditions and diseases.

[000159] "Prostate cancer" is one of the most frequently occurring cancers among men in the United States, with hundreds of thousands of new cases diagnosed each year. Over sixty percent of newly diagnosed cases of prostate cancer are found to be pathologically advanced, with no cure and a dismal prognosis. One third of all men over 50 years of age have a latent form of prostate cancer that may be activated into the life-threatening clinical prostate cancer form. The frequency of latent prostatic tumors has been shown to increase substantially with each decade of life from the 50s (5.3-14%) to the 90s (40-80%). The number of people with latent prostate cancer is the same across all cultures, ethnic groups, and races, yet the frequency of clinically aggressive cancer is markedly different. This suggests that environmental factors may play a role in activating latent prostate cancer.

[000160]

[000161] In one embodiment, the methods of the present invention comprise administering a SARM compound as the sole active ingredient. However, also encompassed within the scope of the present invention are methods for hormone therapy, for treating prostate cancer, for delaying the progression of prostate cancer, and for preventing and/or treating the recurrence of prostate cancer, which comprise administering the SARM compounds in combination with one or more therapeutic agents. These agents include, but are not limited to: LHRH analogs, reversible antiandrogens, antiestrogens, anticancer drugs, 5-alpha reductase inhibitors, aromatase inhibitors, progestins, agents acting through other nuclear hormone receptors, selective estrogen receptor modulators (SERM), progesterone, estrogen, PDE5 inhibitors, apomorphine, bisphosphonate, and one or more additional SARMS.

[000162] Thus, in one embodiment, the methods of the present invention comprise administering the selective androgen receptor modulator compound, in combination with an LHRH analog. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a reversible antiandrogen. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator

compound, in combination with an antiestrogen. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with an anticancer drug. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor  
5 modulator compound, in combination with a 5-alpha reductase inhibitor. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with an aromatase inhibitor. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a progestin. In  
10 another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with an agent acting through other nuclear hormone receptors. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a selective estrogen receptor modulators (SERM). In  
15 another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a progesterone. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with an estrogen. In another embodiment, the methods of the present invention comprise administering a  
20 selective androgen receptor modulator compound, in combination with a PDE5 inhibitor. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with apomorphine. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a  
25 bisphosphonate. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with one or more additional SARMS.

[000163] In one embodiment, the present invention provides a composition  
30 comprising the selective androgen receptor modulator compound of the present invention and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof.

[000164] In another embodiment, the present invention provides a pharmaceutical composition comprising the selective androgen receptor modulator compound of the present invention and/or its analog, derivative, isomer, metabolite, pharmaceutical product, hydrate, N-oxide or any combination thereof; and a suitable carrier or diluent.

[000165] As used herein, "pharmaceutical composition" means therapeutically effective amounts of the SARM together with suitable diluents, preservatives, solubilizers, emulsifiers, adjuvant and/or carriers. A "therapeutically effective amount" as used herein refers to that amount which provides a therapeutic effect for a given condition and administration regimen. Such compositions are liquids or Lyophilized or otherwise dried formulations and include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts), solubilizing agents (e.g., glycerol, polyethylene glycerol), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimerosal, benzyl alcohol, parabens), bulking substances or tonicity modifiers (e.g., lactose, mannitol), covalent attachment of polymers such as polyethylene glycol to the protein, complexation with metal ions, or incorporation of the material into or onto particulate preparations of polymeric compounds such as polylactic acid, polglycolic acid, hydrogels, etc, or onto liposomes, microemulsions, micelles, unilamellar or multilamellar vesicles, erythrocyte ghosts, or spheroplasts.) Such compositions will influence the physical state, solubility, stability, rate of *in vivo* release, and rate of *in vivo* clearance. Controlled or sustained release compositions include formulation in lipophilic depots (e.g., fatty acids, waxes, oils).

[000166] Also comprehended by the invention are particulate compositions coated with polymers (e.g., poloxamers or poloxamines). Other embodiments of the compositions of the invention incorporate particulate forms protective coatings, protease inhibitors or permeation enhancers for various routes of administration, including parenteral, pulmonary, nasal and oral. In one embodiment the pharmaceutical composition is administered parenterally, paracancerally, transmucosally, transdermally,

intramuscularly, intravenously, intradermally, subcutaneously, intraperitoneally, intraventricularly, intravaginally, intracranially and intratumorally.

[000167] Further, as used herein "pharmaceutically acceptable carriers" are well known to those skilled in the art and include, but are not limited to, 0.01-0.1M and preferably 0.05M phosphate buffer or 0.8% saline. Additionally, such pharmaceutically acceptable carriers may be aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media.

[000168] Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's and fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present, such as, for example, antimicrobials, antioxidants, collating agents, inert gases and the like.

[000169] Controlled or sustained release compositions include formulation in lipophilic depots (e.g. fatty acids, waxes, oils). Also comprehended by the invention are particulate compositions coated with polymers (e.g. poloxamers or poloxamines) and the compound coupled to antibodies directed against tissue-specific receptors, ligands or antigens or coupled to ligands of tissue-specific receptors.

[000170] Other embodiments of the compositions of the invention incorporate particulate forms, protective coatings, protease inhibitors or permeation enhancers for various routes of administration, including parenteral, pulmonary, nasal and oral.

[000171] Compounds modified by the covalent attachment of water-soluble polymers such as polyethylene glycol, copolymers of polyethylene glycol and polypropylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol,

polyvinylpyrrolidone or polyproline are known to exhibit substantially longer half-lives in blood following intravenous injection than do the corresponding unmodified compounds (Abuchowski et al., 1981; Newmark et al., 1982; and Katre et al., 1987). Such modifications may also increase the compound's solubility in aqueous solution, eliminate aggregation, enhance the physical and chemical stability of the compound, and greatly reduce the immunogenicity and reactivity of the compound. As a result, the desired *in vivo* biological activity may be achieved by the administration of such polymer-compound adducts less frequently or in lower doses than with the unmodified compound.

10

[000172] In yet another embodiment, the pharmaceutical composition can be delivered in a controlled release system. For example, the agent may be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989). In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in proximity to the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115-138 (1984). Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

20

[000173] The pharmaceutical preparation can comprise the SARM agent alone, or can further include a pharmaceutically acceptable carrier, and can be in solid or liquid form such as tablets, powders, capsules, pellets, solutions, suspensions, elixirs, emulsions, gels, creams, or suppositories, including rectal and urethral suppositories. Pharmaceutically acceptable carriers include gums, starches, sugars, cellulosic materials, and mixtures thereof. The pharmaceutical preparation containing the SARM agent can be administered to a subject by, for example, subcutaneous implantation of a pellet; in a further embodiment, the pellet provides for controlled release of SARM agent over a period of time. The preparation can also be administered by intravenous, intraarterial, or intramuscular injection of a liquid preparation, oral administration of a liquid or solid

30

preparation, or by topical application. Administration can also be accomplished by use of a rectal suppository or a urethral suppository.

[000174] The pharmaceutical preparations of the invention can be prepared by  
5 known dissolving, mixing, granulating, or tablet-forming processes. For oral  
administration, the SARM agents or their physiologically tolerated derivatives such as  
salts, esters, N-oxides, and the like are mixed with additives customary for this purpose,  
such as vehicles, stabilizers, or inert diluents, and converted by customary methods into  
10 suitable forms for administration, such as tablets, coated tablets, hard or soft gelatin  
capsules, aqueous, alcoholic or oily solutions. Examples of suitable inert vehicles are  
conventional tablet bases such as lactose, sucrose, or cornstarch in combination with  
binders such as acacia, cornstarch, gelatin, with disintegrating agents such as cornstarch,  
potato starch, alginic acid, or with a lubricant such as stearic acid or magnesium stearate.

15 [000175] Examples of suitable oily vehicles or solvents are vegetable or animal oils  
such as sunflower oil or fish-liver oil. Preparations can be effected both as dry and as  
wet granules. For parenteral administration (subcutaneous, intravenous, intraarterial, or  
intramuscular injection), the SARM agents or their physiologically tolerated derivatives  
such as salts, esters, N-oxides, and the like are converted into a solution, suspension, or  
20 emulsion, if desired with the substances customary and suitable for this purpose, for  
example, solubilizers or other auxiliaries. Examples are sterile liquids such as water and  
oils, with or without the addition of a surfactant and other pharmaceutically acceptable  
adjuvants. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin,  
for example, peanut oil, soybean oil, or mineral oil. In general, water, saline, aqueous  
25 dextrose and related sugar solutions, and glycols such as propylene glycols or  
polyethylene glycol are preferred liquid carriers, particularly for injectable solutions.

[000176] The preparation of pharmaceutical compositions which contain an active  
component is well understood in the art. Typically, such compositions are prepared as  
30 aerosols of the polypeptide delivered to the nasopharynx or as injectables, either as  
liquid solutions or suspensions; however, solid forms suitable for solution in, or  
suspension in, liquid prior to injection can also be prepared. The preparation can also be



emulsified. The active therapeutic ingredient is often mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol, or the like or any combination thereof.

5

[000177] In addition, the composition can contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents which enhance the effectiveness of the active ingredient.

10

[000178] An active component can be formulated into the composition as neutralized pharmaceutically acceptable salt forms. Pharmaceutically acceptable salts include the acid addition salts (formed with the free amino groups of the polypeptide or antibody molecule), which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed from the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

15

20

[000179] For topical administration to body surfaces using, for example, creams, gels, drops, and the like, the SARM agents or their physiologically tolerated derivatives such as salts, esters, N-oxides, and the like are prepared and applied as solutions, suspensions, or emulsions in a physiologically acceptable diluent with or without a pharmaceutical carrier.

25

[000180] In another embodiment, the active compound can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*).

30

[000181] For use in medicine, the salts of the SARM will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

[000182] The following examples are presented in order to more fully illustrate the preferred embodiments of the invention. They should in no way be construed, however, as limiting the broad scope of the invention.

## **EXPERIMENTAL DETAILS SECTION**

### **Experimental Methods**

#### **Cell Lines**

[000183] The origins of the cell lines used in the studies described herein are shown in Table 1 below:

**Table 1**

Cell line	Morphology	Receptor expressed	Origin	Patient
LNCaP	Epithelial	Androgen; Estrogen	Needle aspiration biopsy of left supraclavicular lymph node	50-year-old white male with stage D1 prostatic cancer
DU 145	Epithelial		Metastatic CNS lesion	69-year-old white male with metastatic carcinoma of the prostate and a 3 year history of lymphocytic leukemia
PC-3	Epithelial		Prostatic metastatic bone marrow	62-year-old male Caucasian with grade IV prostatic adenocarcinoma
PPC-1 (primary prostate carcinoma-1)	Epithelial		Transurethral resection of the prostate	67-year-old black male with stage D2 poorly differentiated adenocarcinoma of prostate
TSU	Epithelial		Metastatic tumor in a cervical lymph	73-year-old male Japanese with a moderately differentiated prostatic adenocarcinoma

			node	
TCCSUP	Epithelial		Anaplastic transitional cell carcinoma in the neck of the urinary bladder	67-year-old female with grade IV bladder cancer
HT-29	Epithelial	Urokinase receptor; Vitamin D	Colorectal adenocarcinoma	44-year-old female caucasian
CV-1	Fibroblast		Normal kidney	Male adult (141 days) African green monkey
MCF-7			Breast adenocarcinoma	

### Cell Growth Conditions

[000184] PPC-1, LNCaP, TSU, PC-3, and DU145 were grown in PRMI-1640 medium containing 2 mM L-glutamine supplemented with 10% fetal bovine serum (FBS). Cells were maintained in a 5% CO<sub>2</sub>/95% air humidified atmosphere at 37°C.

### Sulforhodamine B (SRB) assay

[000185] The SRB Assay was used to determine cell number during cytotoxicity experiments. The following protocol was used:

1. Cells were detached with 0.25% trypsin.
2. Experimental cultures were cultured in 96-well microtiter plates (200uL growth medium per well; 1,000-200,000 cells per well).
3. Cultures were fixed with 50 uL 50% TCA (4 °C). (see cell fixation protocol for details).
4. Fixed cells were stained with 50 uL 0.4% (wt/vol) SRB in 1% acetic acid for 10 minutes.
5. SRB was removed and the cultures were quickly\* rinsed 5 times with 1% acetic acid to remove unbound dye.\*\*
6. Cultures were air-dried overnight until there is no visible moisture.
7. The cellular protein-bound SRB was dissolved with 200 uL unbuffered Tris base (10 mM, pH 10.5) for 30 minutes on a rocking platform shaker.
8. Absorbance was read at 540 nm.

\* quickly performing rinsing process is to prevent desorption of protein-bound SRB

\*\* completely remove residual wash solution by sharply flicking plates over sink.

### Fixation of cells attached to the plastic substratum

5 [000186] The following protocol was used for fixing cells:

- a. 50  $\mu$ L of 50% TCA (4 °C) were gently layered on the top of growth medium in each well to make a final TCA concentration of 10%.
- b. Cultures were incubated at 4 °C for 1 hour.
- c. Cultures were washed 5 times with tap water to remove TCA, growth medium, low-  
10 molecular-weight metabolites, and serum protein.
- d. Plates were air-dried until there was no visible moisture.

### Results

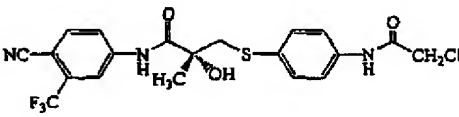
#### EXAMPLE 1

15

### CYTOTOXICITY OF COMPOUNDS IN DIFFERENT CELL LINES

[000187] The  $IC_{50}$ s of R-CTF-T-CA-1, R-CTF-T-BA-1, S-NTBA, Compound V, 5-FU and Taxol in prostate cancer cell lines (DU 145, PC-3, TSU, PPC-1 and LNCaP),  
20 in other cancer cell lines (TCCSUP, HT-29) and in a control cell line (CV-1) are shown in Tables 2A and 2B, and in Figure 1. The results demonstrate that Compound V is highly selective for the AR-expressing LNCaP prostate cancer cell line, compared with other prostate cancer cell lines which do not express the AR, and with non-prostate cancer cell lines. These results demonstrate the potential of Compound V as a useful  
25 agent in prostate cancer monotherapy.

TABLE 2A - Prostate Cancer Cell Lines

Name	Structure	MW	Prostate Cancer Cell Lines				
			DU145	PC-3	TSU	PPC-1	LNCaP
R-CTF-T-CA-1 ( $\mu$ M)		471.88	2.6 $\pm$ 0.1	6.1 $\pm$ 0.5	1.5 $\pm$ 0.2	2.5 $\pm$ 0.1	1.1 $\pm$ 0.2

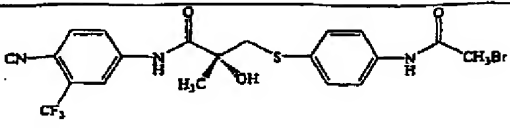
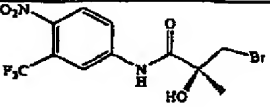
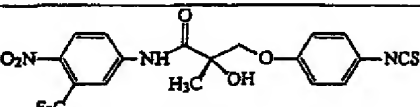
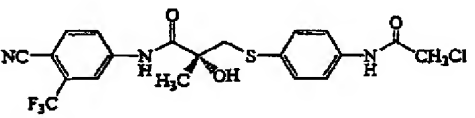
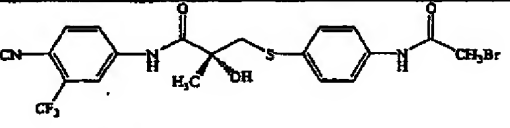
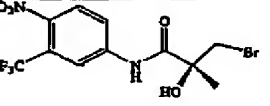
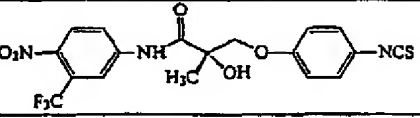
R-CTF-T-BA-1 ( $\mu\text{M}$ )		516.33	3.1 $\pm$ 0.1	2.6 $\pm$ 0.1	0.6 $\pm$ 0.1	1.3 $\pm$ 0.1	3.2 $\pm$ 0.4
S-NTBA ( $\mu\text{M}$ )		371.11	4.7 $\pm$ 0.3	3.1 $\pm$ 0.6	3.5 $\pm$ 0.2	2.2 $\pm$ 0.2	1.4 $\pm$ 0.2
Compound V ( $\mu\text{M}$ )		421.39	74.8 $\pm$ 1.2	59.0 $\pm$ 6	56.9 $\pm$ 2.9	58.1 $\pm$ 5.9	26.0 $\pm$ 8.3
5-FU ( $\mu\text{M}$ )		130.1	4.5 $\pm$ 0.3	10.5 $\pm$ 0.6	2.7 $\pm$ 0.6	5.1 $\pm$ 0.5	4.1 $\pm$ 0.6
Taxol (nM)		853.9	2.7 $\pm$ 0.3	6.3 $\pm$ 0.6	2.4 $\pm$ 0.8	2.7 $\pm$ 0.3	1.9 $\pm$ 0.3

TABLE 2B – Other Cancer Cell Lines and Control

Name	Structure	MW	<u>Other Cancer Cell Lines and Control</u>		
			TCCSUP	HT-29	CV-1 (Control)
R-CTF-T-CA-1 ( $\mu\text{M}$ )		471.88	1.8 $\pm$ 0.2	6.4 $\pm$ 0.5	2.7 $\pm$ 1.0
R-CTF-T-BA-1 ( $\mu\text{M}$ )		516.33	3.8 $\pm$ 0.5	1.6 $\pm$ 0.03	10.8 $\pm$ 0.5
S-NTBA ( $\mu\text{M}$ )		371.11	2.4 $\pm$ 0.3	6.3 $\pm$ 0.3	12.7 $\pm$ 0.3
Compound V ( $\mu\text{M}$ )		421.39	>100	55.0 $\pm$ 1.7	NA
5-FU ( $\mu\text{M}$ )		130.1	3.6 $\pm$ 0.7	5.4 $\pm$ 1.1	5.4 $\pm$ 0.3
Taxol (nM)		853.9	4.3 $\pm$ 0.6	6.6 $\pm$ 0.6	

**EXAMPLE 2****CYTOTOXICITY OF COMPOUNDS IN LNCaP CELL LINE**

5 [000188] The IC<sub>50</sub>s of R-CTF-T-CA-1, R-CTF-T-BA-1, S-NTBA, and Compound V in AR-expressing LNCaP Prostate Cancer cell line and in a control cell line (CV-1) are shown in Table 3 and in Figure 2 (LNCaP) and Figure 3 (CV-1). Following 24 hr treatment, the IC<sub>50</sub>s of R-CTF-T-BA-1, R-CTF-T-CA1, S-NTBA and Compound V in the LNCaP cell line were 11.2 μM, 3.5 μM, 4.4 μM and 39.6 μM, respectively. Following a

10 6 day treatment, the IC<sub>50</sub>s of R-CTF-T-BA-1, R-CTF-T-CA1, S-NTBA and Compound V in the LNCaP cell line were 8.1 μM, 1.7 μM, 2.1 μM and 33.6 μM, respectively. This is compared with the results in a control CV-1 cell line, in which the IC<sub>50</sub>s of R-CTF-T-BA-1, R-CTF-T-CA1, and S-NTBA following a 4 day treatment were 13.9 μM, 4.2 μM, and 4.9 μM respectively (Compound V – NA). The results demonstrate that Compound V is

15 highly selective for the AR-expressing LNCaP prostate cancer cell line, compared with a control cell line. These results demonstrate the potential of Compound V as a useful agent in prostate cancer monotherapy.

**TABLE 3- Different Treatment of R-CTFs on LNCaP and CV-1**

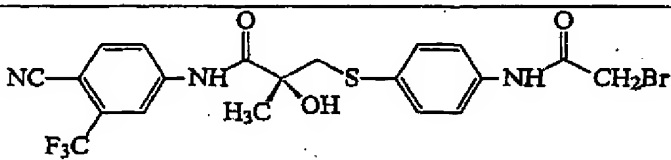
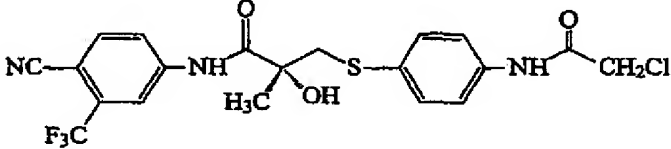
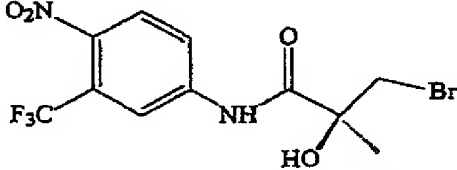
Name	Structure	LNCaP (μM)		CV-1 (μM)	
		24 hr treatment	6 day treatment	24 hr treatment	4 day treatment
R-CTF-T-BA-1		11.2±4.6 (9-10-01)	8.1±0.8 (9-8-01)	23.4±1.6 (9-11-01)	13.9±0.8 (9-11-01)
R-CTF-T-CA-1		3.5±1.9 (9-10-01)	1.7±0.1 (9-8-01)	6.2±0.2 (9-11-01)	4.2±0.1 (9-11-01)
S-NTBA		4.4±2.0 (9-10-01)	2.1±0.2 (9-8-01)	48.2±10.9 (9-11-01)	4.9±0.5 (9-11-01)
Compound V		39.6±2.7 (9-10-01)	33.6±6.9 (9-8-01)	NA (9-11-01)	NA (9-11-01)

20

**EXAMPLE 3****CYTOTOXICITY OF COMPOUNDS IN PC-3 CELL LINE**

5 [000189] The  $IC_{50}$ s of R-CTF-T-CA-1, R-CTF-T-BA-1, S-NTBA, and 5-FU in PC-3 Prostatic metastatic bone marrow cell line are shown in Table 4 and in Figure 4. Following 24 hr treatment, the  $IC_{50}$ s of R-CTF-T-BA-1, R-CTF-T-CA1, S-NTBA and 5-FU were 22.1  $\mu$ M, 5.8  $\mu$ M, >50  $\mu$ M and 22-50  $\mu$ M, respectively. Following a 4 day treatment, the  $IC_{50}$ s of R-CTF-T-BA-1, R-CTF-T-CA1, S-NTBA and 5-FU were 16.8  $\mu$ M, 4.3  $\mu$ M, 18.0  $\mu$ M and 10.9  $\mu$ M, respectively.

**TABLE 4- Summary of  $IC_{50}$ s of R-CTF-Ts on PC-3 from different treatments**

Name	Structure	$IC_{50}$ ( $\mu$ M)	
		24 hr treatment	4 day treatment
R-CTF-T-BA-1		22.1	16.8
R-CTF-T-CA-1		5.8	4.3
S-NTBA		>50	18.0
5-FU		20-50	10.9

15

### EXAMPLE 4

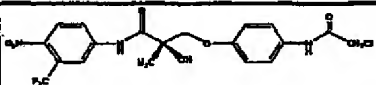
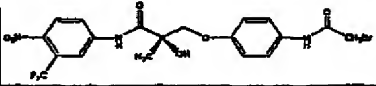
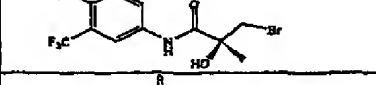

### EXTENDED CYTOTOXICITY STUDIES OF COMPOUNDS IN DIFFERENT CELL LINES

5

[000190] The IC<sub>50</sub>s of DJ 1-31, DJ 1-29, S-NTBA and Compound V in different prostate cancer cell lines (DU 145, PC-3, TSU, PPC-1 and LNCaP), in other cancer cell lines (TCCSUP, HT-29 and MCF-7) and in a control cell line (CV-1) after 1 and 4 days of incubation with the drug, are shown in Tables 5 A and B. The results demonstrate that Compound V is highly selective for the AR-expressing LNCaP prostate cancer cell line, compared with other prostate cancer cell lines which do not express the AR, and with non-prostate cancer cell lines. These results demonstrate the potential of Compound V as a useful agent in prostate cancer monotherapy.

15

**TABLE 5A – Prostate Cancer Cell Lines**

Cpd ID	Structure	drug incubation time (day)	IC <sub>50</sub> (uM)				
			LNCaP	DU 145	PC-3	PPC-1	TSU
DJ 1-31		1	2.9±1.2	1.0±0.2	5.4±0.8	1.9±0.1	1.3±0.1
		4	3.3±0.4	0.7±0.1	5.3±0.8	1.9±0.1	1.1±0.1
DJ 1-29		1	1.1±0.4	0.4±0.1	2.3±0.1	0.9±0.1	1.3±0.1
		4	1.8±0.2	0.4±0.1	2.4±0.4	1.3±0.1	1.0±0.1
S-NTBA		1	1.6±0.3	5.5±0.6	7.9±0.7	1.7±0.2	4.9±0.4
		4	1.8±0.9	4.6±0.8	3.7±1.1	2.7±0.8	2.9±0.2
V		1	19.8±10.5	62.1±0.6	47.8±4.2	63.7±4.6	54.1±5.5
		4	12.8±4.1	69.7±6.5	48.5±10.1	62.6±4.9	55.0±0.8

20



TABLE 5B – Other Cancer Cell Lines and Control

Cpd ID	Structure	drug incubation time (day)	IC <sub>50</sub> (uM)			
			HT-29	TCCSUP	MCF-7	CV-1
DJ 1-31		1	5.4±0.1	2.1±0.3	15.8±2.7	5.8±0.3
		4	3.7±0.7	2.1±0.3	14.0±1.1	5.3±0.2
DJ 1-29		1	3.6±0.4	2.6±0.4	11.9±0.3	6.8±0.5
		4	4.4±0.2	2.5±0.4	12.9±0.7	7.3±0.2
S-NTBA		1	19.8±1.0	9.5±3.6	3.3±0.6	>50
		4	10.8±0.4	4.6±0.3	3.3±2.0	38.6±3.6
V		1	85.5±4.5	90.4±2.2	32.7±1.9	>100
		4	71.0±1.2	78.1±11.2	39.4±5.4	>100

5

**EXAMPLE 5****EFFECT OF COMPOUNDS ON APOPTOSIS IN DIFFERENT CELL LINES**

10

[000191] The ability of DJ 1-31, DJ 1-29, S-NTBA and Compound V to induce apoptosis in different prostate cancer cell lines (DU 145, PC-3, TSU, PPC-1 and LNCaP), in other cancer cell lines (TCCSUP, HT-29 and MCF-7) and in a control cell line (CV-1) was determined and the results are shown in Table 6.

15

**TABLE 6:**

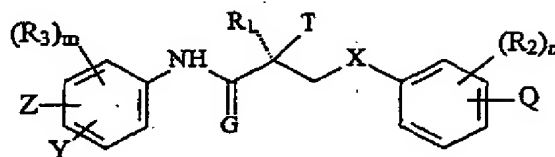
Cpd ID	Structure	Enrichment factor								
		LNCaP	DU 145	PC-3	PPC-1	TSU	HT-29	TCCSUP	MCF-7	CV-1
DJ 1-31		1.374	2.500	0.594	1.312	0.848	1.205	0.471	0.938	0.702
DJ 1-29		16.571	18.643	0.531	1.146	1.008	1.667	0.000	1.617	0.786
S-NTBA		0.660	1.929	0.750	0.697	0.705	1.538	0.118	2.012	0.393
CK 1-85		2.000	5.071	2.500	1.749	1.167	1.410	1.176	1.926	6.546

[000192] It will be appreciated by a person skilled in the art that the present invention is not limited by what has been particularly shown and described hereinabove. Rather, the scope of the invention is defined by the claims that follow:

5

**WHAT IS CLAIMED IS:**

1. A selective androgen receptor modulator (SARM) compound represented by the structure of formula I:



I

X is a bond, O, CH<sub>2</sub>, NH, S, Se, PR, NO or NR;

G is O or S;

T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR;

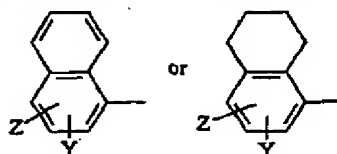
R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH;

R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;

R<sub>2</sub> is F, Cl, Br, I, CH<sub>3</sub>, CF<sub>3</sub>, OH, CN, NO<sub>2</sub>, NHCOCH<sub>3</sub>, NHCOCF<sub>3</sub>, NHCOR, alkyl, arylalkyl, OR, NH<sub>2</sub>, NHR, NR<sub>2</sub>, SR;

R<sub>3</sub> is F, Cl, Br, I, CN, NO<sub>2</sub>, COR, COOH, CONHR, CF<sub>3</sub>, SnR<sub>3</sub>, or

R<sub>3</sub> together with the benzene ring to which it is attached forms a fused ring system represented by the structure:



Z is NO<sub>2</sub>, CN, COR, COOH, or CONHR;

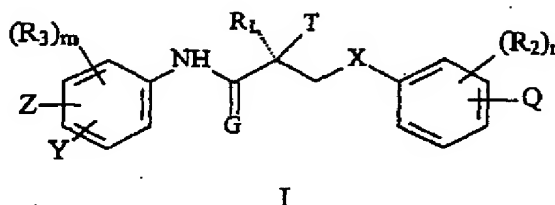
Y is CF<sub>3</sub>, F, Br, Cl, I, CN, or SnR<sub>3</sub>;

Q is SCN, NCS, OCN, or NCO;

n is an integer of 1-4; and

m is an integer of 1-3.

2. A selective androgen receptor modulator (SARM) compound represented by the structure of formula I:



X is a bond, O, CH<sub>2</sub>, NH, S, Se, PR, NO or NR;

G is O or S;

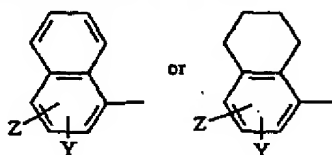
T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH;

R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;

R<sub>2</sub> is F, Cl, Br, I, CH<sub>3</sub>, CF<sub>3</sub>, OH, CN, NO<sub>2</sub>, NHCOCH<sub>3</sub>, NHCOCF<sub>3</sub>, NHCOR, alkyl, arylalkyl, OR, NH<sub>2</sub>, NHR, NR<sub>2</sub>, SR;

R<sub>3</sub> is F, Cl, Br, I, CN, NO<sub>2</sub>, COR, COOH, CONHR, CF<sub>3</sub>, SnR<sub>3</sub>, or R<sub>3</sub> together with the benzene ring to which it is attached forms a fused ring system represented by the structure:



Z is NO<sub>2</sub>, CN, COR, COOH, or CONHR;

Y is CF<sub>3</sub>, F, Br, Cl, I, CN, or SnR<sub>3</sub>;

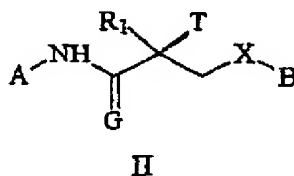
Q is SCN, NCS, OCN, or NCO;

n is an integer of 1-4; and

m is an integer of 1-3;

or its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

3. The compound according to claim 1, wherein G is O.
4. The compound according to claim 1, wherein T is OH.
5. The compound according to claim 1, wherein R<sub>1</sub> is CH<sub>3</sub>.
- 5 6. The compound according to claim 1, wherein X is O.
7. The compound according to claim 1, wherein Z is NO<sub>2</sub>.
8. The compound according to claim 1, wherein Z is CN.
9. The compound according to claim 1, wherein Y is CF<sub>3</sub>.
10. The compound according to claim 1, wherein Q is NCS.
- 10 11. The compound according to claim 1, wherein G is O, T is OH, R<sub>1</sub> is CH<sub>3</sub>, X is O, Z is NO<sub>2</sub>, Y is CF<sub>3</sub>, and Q is NCS.
12. The compound according to claim 1, wherein said compound is an androgen receptor antagonist.
13. The compound according to claim 1, wherein said compounds binds irreversibly to an androgen receptor.
- 15 14. The compound according to claim 1, wherein said compound is an androgen receptor antagonist which binds irreversibly to an androgen receptor.
- 15 15. A selective androgen receptor modulator (SARM) compound represented by the structure of formula II:
- 20



wherein X is a bond, O, CH<sub>2</sub>, NH, S, Se, PR, NO or NR;

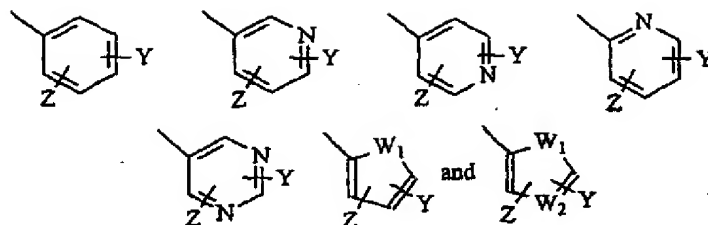
G is O or S;

25 R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;

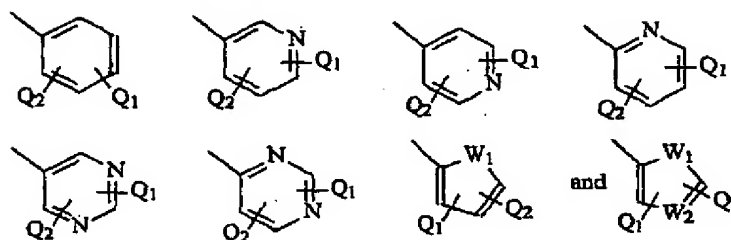
T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH;

A is a ring selected from:



B is a ring selected from:



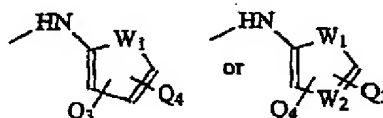
wherein A and B cannot simultaneously be a benzene ring;

Z is NO<sub>2</sub>, CN, COOH, COR, NHCOR or CONHR;

Y is CF<sub>3</sub>, F, I, Br, Cl, CN CR<sub>3</sub> or SnR<sub>3</sub>;

Q<sub>1</sub> is NCS, SCN, NCO or OCN;

Q<sub>2</sub> is a hydrogen, alkyl, halogen, CF<sub>3</sub>, CN CR<sub>3</sub>, SnR<sub>3</sub>, NR<sub>2</sub>, NHCOCH<sub>3</sub>,  
NHCOCF<sub>3</sub>, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR,  
NHCSCH<sub>3</sub>, NHCSCF<sub>3</sub>, NHCSR NHSO<sub>2</sub>CH<sub>3</sub>, NHSO<sub>2</sub>R, OR, COR,  
OCOR, OSO<sub>2</sub>R, SO<sub>2</sub>R, SR,

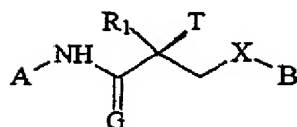


Q<sub>3</sub> and Q<sub>4</sub> are independently of each other a hydrogen, alkyl,  
halogen, CF<sub>3</sub>, CN CR<sub>3</sub>, SnR<sub>3</sub>, NR<sub>2</sub>, NHCOCH<sub>3</sub>, NHCOCF<sub>3</sub>, NHCOR,  
NHCONHR, NHCOOR, OCONHR, CONHR, NHCSCH<sub>3</sub>, NHCSCF<sub>3</sub>,  
NHCSR NHSO<sub>2</sub>CH<sub>3</sub>, NHSO<sub>2</sub>R, OR, COR, OCOR, OSO<sub>2</sub>R, SO<sub>2</sub>R or SR;

W<sub>1</sub> is O, NH, NR, NO or S; and

W<sub>2</sub> is N or NO.

16. A selective androgen receptor modulator (SARM) compound represented by the structure of formula II:



II

wherein X is a bond, O, CH<sub>2</sub>, NH, S, Se, PR, NO or NR;

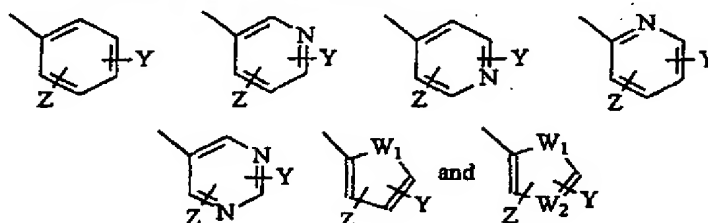
G is O or S;

5 R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;

T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR;

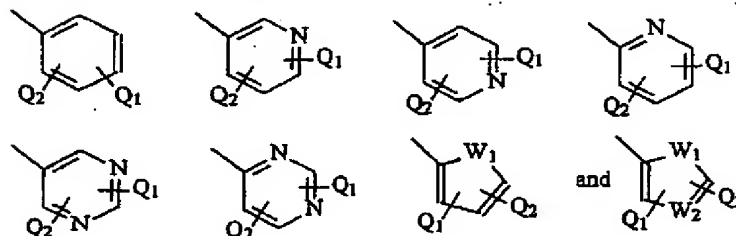
R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH;

A is a ring selected from:



10

B is a ring selected from:



wherein A and B cannot simultaneously be a benzene ring;

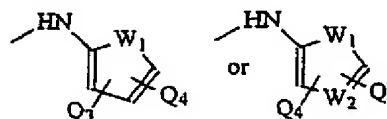
Z is NO<sub>2</sub>, CN, COOH, COR, NHCOR or CONHR;

15 Y is CF<sub>3</sub>, F, I, Br, Cl, CN CR<sub>3</sub> or SnR<sub>3</sub>;

Q<sub>1</sub> is NCS, SCN, NCO or OCN;

Q<sub>2</sub> is a hydrogen, alkyl, halogen, CF<sub>3</sub>, CN CR<sub>3</sub>, SnR<sub>3</sub>, NR<sub>2</sub>, NHCOCH<sub>3</sub>, NHCOCF<sub>3</sub>, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, NHCSCH<sub>3</sub>, NHCSCF<sub>3</sub>, NHCSR, NHSO<sub>2</sub>CH<sub>3</sub>, NHSO<sub>2</sub>R, OR, COR, OCOR, OSO<sub>2</sub>R, SO<sub>2</sub>R, SR,

20



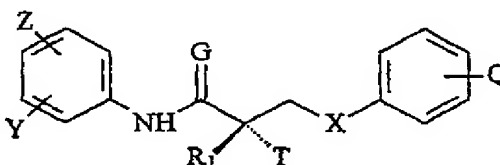
$Q_3$  and  $Q_4$  are independently of each other a hydrogen, alkyl, halogen,  $CF_3$ ,  $CN$ ,  $CR_3$ ,  $SnR_3$ ,  $NR_2$ ,  $NHCOCH_3$ ,  $NHCOCF_3$ ,  $NHCOR$ ,  $NHCONHR$ ,  $NHCOOR$ ,  $OCONHR$ ,  $CONHR$ ,  $NHCSCH_3$ ,  $NHCSCF_3$ ,  $NHCSR$ ,  $NHSO_2CH_3$ ,  $NHSO_2R$ ,  $OR$ ,  $COR$ ,  $OCOR$ ,  $OSO_2R$ ,  $SO_2R$  or  $SR$ ;

5  $W_1$  is O, NH, NR, NO or S; and

$W_2$  is N or NO.

or its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

- 10 17. The compound according to claim 15, wherein G is O.
18. The compound according to claim 15, wherein T is OH.
19. The compound according to claim 15, wherein  $R_1$  is  $CH_3$ .
20. The compound according to claim 15, wherein X is O.
21. The compound according to claim 15, wherein Z is  $NO_2$ .
- 15 22. The compound according to claim 15, wherein Z is CN.
23. The compound according to claim 15, wherein Y is  $CF_3$ .
24. The compound according to claim 15, wherein  $Q_1$  is NCS.
25. The compound according to claim 15, wherein G is O, T is OH,  $R_1$  is  $CH_3$ , X is O, Z is  $NO_2$ , Y is  $CF_3$ , and  $Q_1$  is NCS.
- 20 26. The compound according to claim 15, wherein said compound is an androgen receptor antagonist.
27. The compound according to claim 15, wherein said compounds binds irreversibly to an androgen receptor.
28. The compound according to claim 15, wherein said compound is an androgen
- 25 receptor antagonist which binds irreversibly to an androgen receptor.
29. A selective androgen receptor modulator (SARM) compound represented by the structure of formula III:

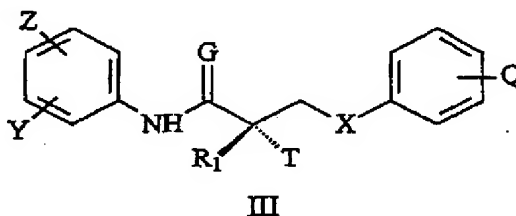


III



wherein X is a bond, O, CH<sub>2</sub>, NH, S, Se, PR, NO or NR;  
 G is O or S;  
 T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR  
 Z is NO<sub>2</sub>, CN, COOH, COR, NHCOR or CONHR;  
 Y is CF<sub>3</sub>, F, I, Br, Cl, CN, CR<sub>3</sub> or SnR<sub>3</sub>;  
 Q is SCN, NCS, OCN, or NCO;  
 R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>,  
 CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH; and  
 R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>.

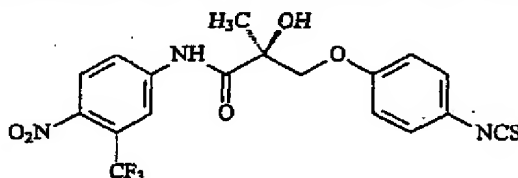
30. A selective androgen receptor modulator (SARM) compound represented by the structure of formula III:



- wherein X is a bond, O, CH<sub>2</sub>, NH, S, Se, PR, NO or NR;  
 G is O or S;  
 T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR  
 Z is NO<sub>2</sub>, CN, COOH, COR, NHCOR or CONHR;  
 Y is CF<sub>3</sub>, F, I, Br, Cl, CN, CR<sub>3</sub> or SnR<sub>3</sub>;  
 Q is SCN, NCS, OCN, or NCO;  
 R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>,  
 CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH; and  
 R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;  
 or its analog, isomer, metabolite, derivative, pharmaceutically acceptable  
 salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

31. The compound according to claim 29, wherein G is O.  
 32. The compound according to claim 29, wherein T is OH.  
 33. The compound according to claim 29, wherein R<sub>1</sub> is CH<sub>3</sub>.  
 34. The compound according to claim 29, wherein X is O.

35. The compound according to claim 29, wherein Z is NO<sub>2</sub>.
36. The compound according to claim 29, wherein Z is CN.
37. The compound according to claim 29, wherein Y is CF<sub>3</sub>.
38. The compound according to claim 29, wherein Q is NCS.
- 5 39. The compound according to claim 29, wherein G is O, T is OH, R<sub>1</sub> is CH<sub>3</sub>, X is O, Z is NO<sub>2</sub>, Y is CF<sub>3</sub>, and Q is NCS.
40. The compound according to claim 29, wherein said compound is an androgen receptor antagonist.
41. The compound according to claim 29, wherein said compounds binds irreversibly to an androgen receptor.
- 10 42. The compound according to claim 29, wherein said compound is an androgen receptor antagonist which binds irreversibly to an androgen receptor.
43. The compound according to claim 29, represented by the structure of formula V:



15

V

44. A composition comprising the selective androgen receptor modulator compound of claim 1, 15, 29 or 43 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof; and a suitable carrier or diluent.
- 20 45. A pharmaceutical composition comprising an effective amount of the selective androgen receptor modulator compound of claim 1, 15, 29 or 43 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof; and a pharmaceutically acceptable carrier, diluent or salt.
- 25 46. A method of binding a selective androgen receptor modulator compound to an androgen receptor, comprising the step of contacting the androgen receptor with the selective androgen receptor modulator compound of claim 1, 15, 29 or 43 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an

amount effective to bind the selective androgen receptor modulator compound to the androgen receptor.

- 5 47. A method of irreversibly binding a selective androgen receptor modulator compound to an androgen receptor, comprising the step of contacting the androgen receptor with the selective androgen receptor modulator compound of claim 1, 15, 29 or 43 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to irreversibly bind the selective androgen receptor modulator compound to the androgen receptor.
- 10 48. A method of alkylating an androgen receptor, comprising the step of contacting the androgen receptor with the selective androgen receptor modulator compound of claim 1, 15, 29 or 43 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to alkylate the androgen receptor.
- 15 49. A method of suppressing spermatogenesis in a subject comprising contacting an androgen receptor of the subject with the selective androgen receptor modulator compound of claim 1, 15, 29 or 43 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to suppress sperm production.
- 20 50. A method of contraception in a male subject, comprising the step of administering to said subject the selective androgen receptor modulator compound of claim 1, 15, 29 or 43 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to suppress sperm production in said subject, thereby effecting contraception in said subject.
- 25 51. A method of hormone therapy comprising the step of contacting an androgen receptor of a subject with the selective androgen receptor modulator compound of claim 1, 15, 29 or 43 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to effect a change in an androgen-dependent condition.
- 30

52. A method of hormone replacement therapy comprising the step of contacting an androgen receptor of a subject with the selective androgen receptor modulator compound of claim 1, 15, 29 or 43 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to effect a change in an androgen-dependent condition.
53. A method of preventing prostate cancer in a subject, comprising the step of administering to said subject the selective androgen receptor modulator compound of claim 1, 15, 29 or 43 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to prevent prostate cancer in said subject.
54. A method of treating a subject having a hormone related condition, comprising the step of administering to said subject the selective androgen receptor modulator compound of claim 1, 15, 29 or 43 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to effect a change in an androgen-dependent condition.
55. A method of treating a subject suffering from prostate cancer, comprising the step of administering to said subject the selective androgen receptor modulator compound of claim 1, 15, 29 or 43 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to treat prostate cancer in said subject.
56. A method of delaying the progression of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to said subject the selective androgen receptor modulator compound of claim 1, 15, 29 or 43 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to delay the progression of prostate cancer in said subject.
57. A method of preventing the recurrence of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to said subject the

selective androgen receptor modulator compound of claim 1, 15, 29 or 43 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to prevent the recurrence of prostate cancer in said subject.

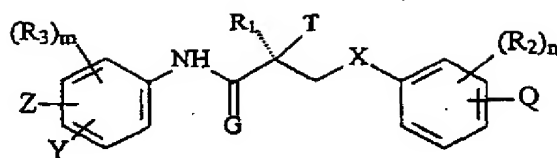
5 58. A method of treating the recurrence of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to said subject the selective androgen receptor modulator compound of claim 1, 15, 29 or 43 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to  
10 treat the recurrence of prostate cancer in said subject.

59. A method of treating a dry eye condition in a subject suffering from dry eyes, comprising the step of administering to said subject the selective androgen receptor modulator compound of claim 1, 15, 29 or 43 06 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical  
15 product, hydrate or N-oxide or any combination thereof, in an amount effective to treat dry eyes in the subject.

60. A method of preventing a dry eye condition in a subject, comprising the step of administering to said subject the selective androgen receptor modulator compound of claim 1, 15, 29 or 43 and/or its analog, derivative, isomer, metabolite,  
20 pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to prevent dry eyes in the subject.

61. A method of inducing apoptosis in a prostate cancer cell, comprising the step of contacting said cell with the selective androgen receptor modulator compound of claim 1, 15, 29 or 43 and/or its analog, derivative, isomer, metabolite,  
25 pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to induce apoptosis in said cancer cell.

62. A process for preparing a selective androgen receptor modulator (SARM)  
30 compound represented by the structure of formula I:



I

wherein X is a O, NH, S, Se, PR, or NR;

G is O or S;

5

T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR;

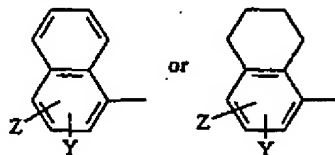
R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH;

R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;

10

R<sub>2</sub> is F, Cl, Br, I, CH<sub>3</sub>, CF<sub>3</sub>, OH, CN, NO<sub>2</sub>, NHCOCH<sub>3</sub>, NHCOCF<sub>3</sub>, NHCOR, alkyl, arylalkyl, OR, NH<sub>2</sub>, NHR, NR<sub>2</sub>, SR;

R<sub>3</sub> is F, Cl, Br, I, CN, NO<sub>2</sub>, COR, COOH, CONHR, CF<sub>3</sub>, SnR<sub>3</sub>, or R<sub>3</sub> together with the benzene ring to which it is attached forms a fused ring system represented by the structure:



15

Z is NO<sub>2</sub>, CN, COR, COOH, or CONHR;

Y is CF<sub>3</sub>, F, Br, Cl, I, CN, or SnR<sub>3</sub>;

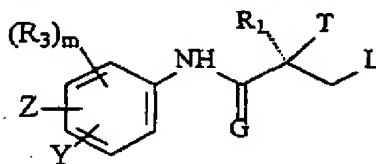
Q is SCN, NCS, OCN, or NCO;

n is an integer of 1-4; and

20

m is an integer of 1-3;

said process comprising the step of coupling a compound of formula VIII:

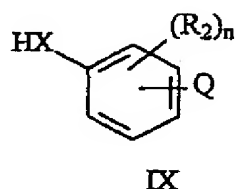


VIII

25

wherein Z, Y, G, R<sub>1</sub>, T, R<sub>3</sub> and m are as defined above and L is a leaving group,

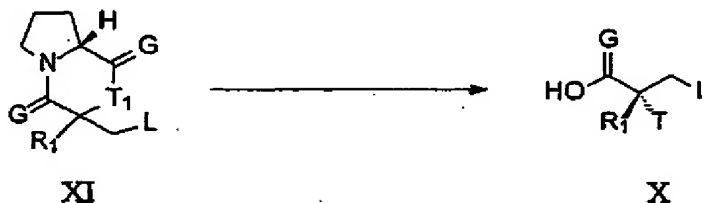
with a compound of formula IX:



5 wherein O, X R<sub>2</sub> and n are as defined above.

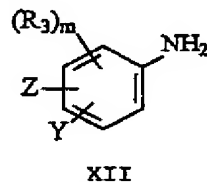
63. The process according to claim 62, wherein G is O, T is OH, R<sub>1</sub> is CH<sub>3</sub>, X is O, Z is NO<sub>2</sub>, Y is CF<sub>3</sub>, and Q is NCS.
- 10 64. The process according to claim 62, wherein the compound of formula VIII is prepared by

a) preparing a compound of formula X by ring opening of a cyclic compound of formula XI

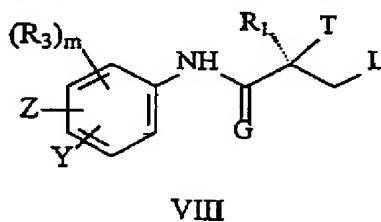


wherein L, R<sub>1</sub>, G and T are as defined above, and T<sub>1</sub> is O or NH; and

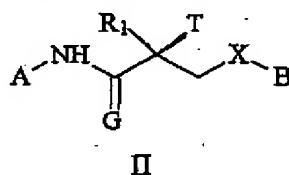
b) reacting an amine of formula XII:



20            wherein Z, Y, R<sub>3</sub> and m are as defined above, with the compound of formula X, in the presence of a coupling reagent, to produce the compound of formula VIII.



65. The process according to claim 62, further comprising the step of purifying said compound of formula I using a mixture of ethanol and water.
66. The process according to claim 62, further comprising the step of converting said selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.
67. A process for preparing a selective androgen receptor modulator (SARM) compound represented by the structure of formula II:



wherein X is O, NH, S, Se, PR, or NR;

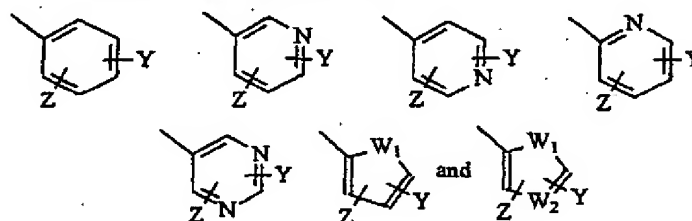
G is O or S;

R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;

T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR;

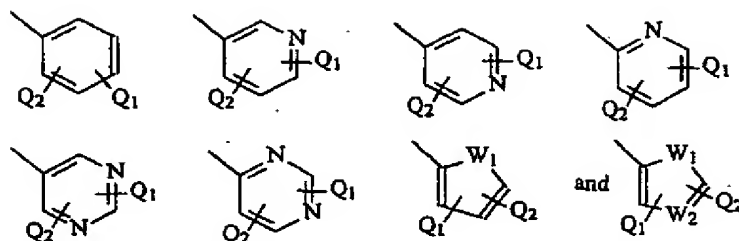
R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH;

A is a ring selected from:



B is a ring selected from:





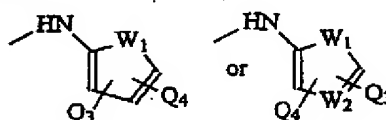
wherein A and B cannot simultaneously be a benzene ring;

Z is NO<sub>2</sub>, CN, COOH, COR, NHCOR or CONHR;

Y is CF<sub>3</sub>, F, I, Br, Cl, CN CR<sub>3</sub> or SnR<sub>3</sub>;

Q<sub>1</sub> is NCS, SCN, NCO or OCN;

Q<sub>2</sub> is a hydrogen, alkyl, halogen, CF<sub>3</sub>, CN CR<sub>3</sub>, SnR<sub>3</sub>, NR<sub>2</sub>, NHCOCH<sub>3</sub>, NHCOCF<sub>3</sub>, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, NHCSCH<sub>3</sub>, NHCSCF<sub>3</sub>, NHCSR, NHSO<sub>2</sub>CH<sub>3</sub>, NHSO<sub>2</sub>R, OR, COR, OCOR, OSO<sub>2</sub>R, SO<sub>2</sub>R, SR,

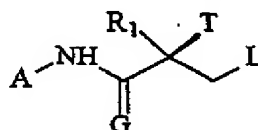


Q<sub>3</sub> and Q<sub>4</sub> are independently of each other a hydrogen, alkyl, halogen, CF<sub>3</sub>, CN CR<sub>3</sub>, SnR<sub>3</sub>, NR<sub>2</sub>, NHCOCH<sub>3</sub>, NHCOCF<sub>3</sub>, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, NHCSCH<sub>3</sub>, NHCSCF<sub>3</sub>, NHCSR, NHSO<sub>2</sub>CH<sub>3</sub>, NHSO<sub>2</sub>R, OR, COR, OCOR, OSO<sub>2</sub>R, SO<sub>2</sub>R or SR;

W<sub>1</sub> is O, NH, NR, NO or S; and

W<sub>2</sub> is N or NO;

said process comprising the step of coupling a compound of formula XIII:



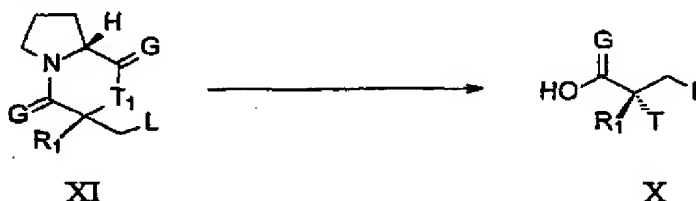
XIII

wherein A, G, R<sub>1</sub> and T are as defined above and L is a leaving group, with a compound of formula HX-B wherein B and X are as defined above.

68. The process according to claim 67, wherein G is O, T is OH, R<sub>1</sub> is CH<sub>3</sub>, X is O, Z is NO<sub>2</sub>, Y is CF<sub>3</sub>, and Q<sub>1</sub> is NCS.

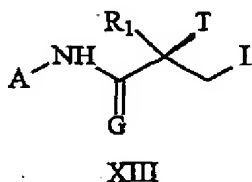
69. The process according to claim 67, wherein the amide of formula XIII is prepared by

- a) preparing a compound formula X by ring opening of a cyclic compound of formula XI

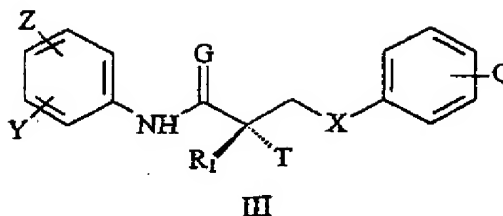


wherein L, R<sub>1</sub>, G and T are as defined above, and T<sub>1</sub> is O or NH; and

- b) reacting an amine of formula A-NH<sub>2</sub> wherein A is as defined above, with the compound of formula X in the presence of a coupling reagent, to produce the amide of formula XIII.



70. The process according to claim 67, further comprising the step of purifying said compound of formula II using a mixture of ethanol and water
71. The process according to claim 67, further comprising the step of converting said selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.
72. A process for preparing a selective androgen receptor modulator (SARM) compound represented by the structure of formula III:



wherein X is O, NH, S, Se, PR or NR;

G is O or S;

T is OH, OR, -NHCOCH<sub>3</sub>, or NHCOR

Z is NO<sub>2</sub>, CN, COOH, COR, NHCOR or CONHR;

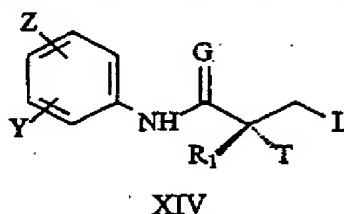
Y is CF<sub>3</sub>, F, I, Br, Cl, CN, CR<sub>3</sub> or SnR<sub>3</sub>;

Q is SCN, NCS, OCN, or NCO;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, aryl, phenyl, halogen, alkenyl or OH; and

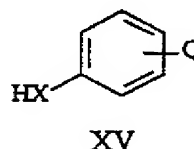
R<sub>1</sub> is CH<sub>3</sub>, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CF<sub>2</sub>CF<sub>3</sub>;

said process comprising the step of coupling a compound of formula XIV:



wherein Z, Y, G R<sub>1</sub> and T are as defined above and L is a leaving group,

with a compound of formula XV:

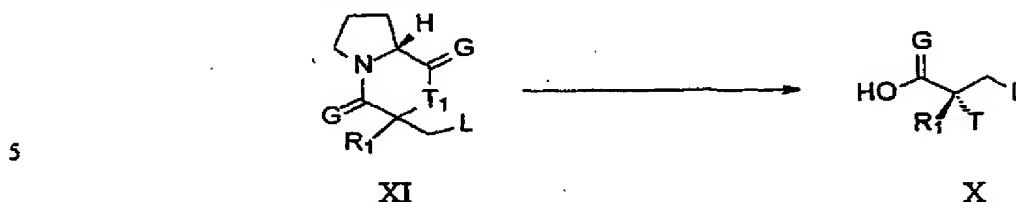


wherein Q and X are as defined above.

73. The process according to claim 72, wherein G is O, T is OH, R<sub>1</sub> is CH<sub>3</sub>, X is O, Z is NO<sub>2</sub>, Y is CF<sub>3</sub>, and Q is NCS.

74. The process according to claim 72, wherein the compound of formula XIV is prepared by

a) preparing a compound formula X by ring opening of a cyclic compound of formula XI

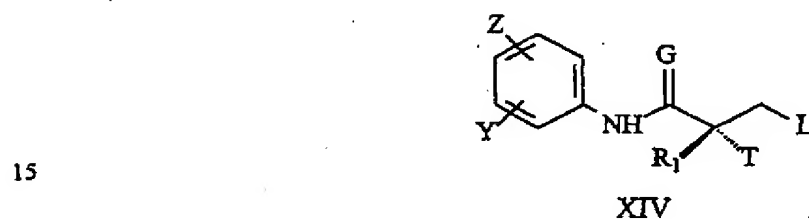


wherein L, R<sub>1</sub>, and T are as defined above, G is O and T<sub>1</sub> is O or NH; and

b) reacting an amine of formula XVI



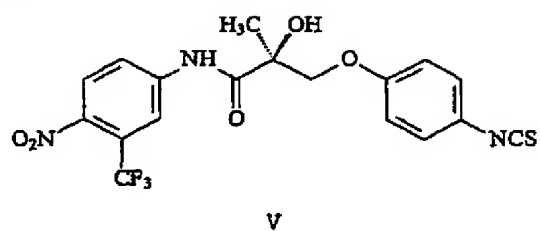
with the compound of formula X in the presence of a coupling reagent, to produce the compound of formula XIV.



20 75. The process according to claim 72, further comprising the step of purifying said compound of formula III using a mixture of ethanol and water

76. The process according to claim 72, further comprising the step of converting said selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

77. The process according to claim 72, wherein said SARM is represented by the structure of formula V:



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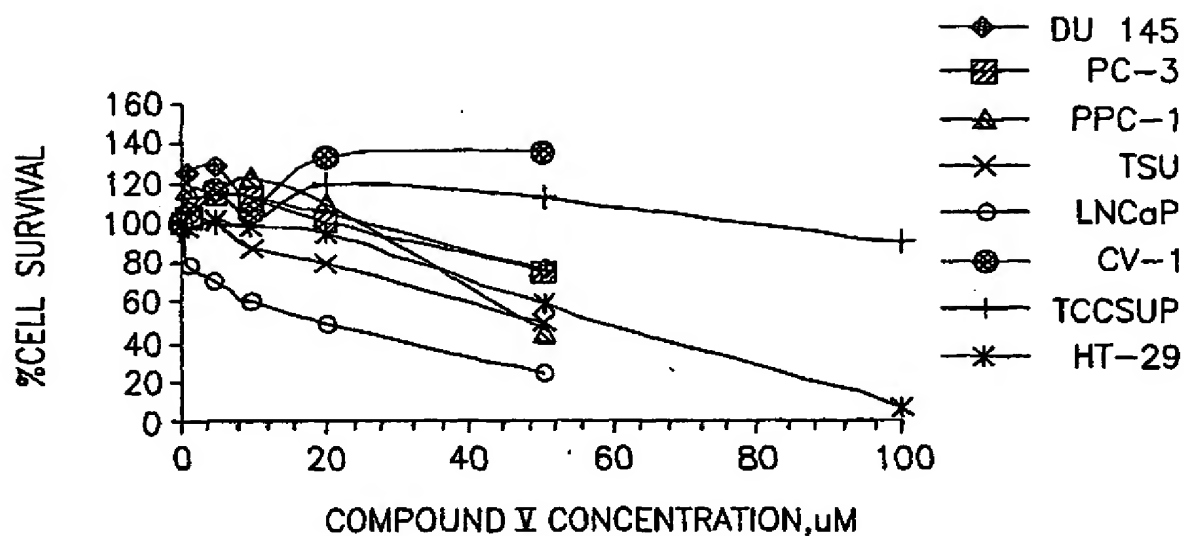


FIG. 1A

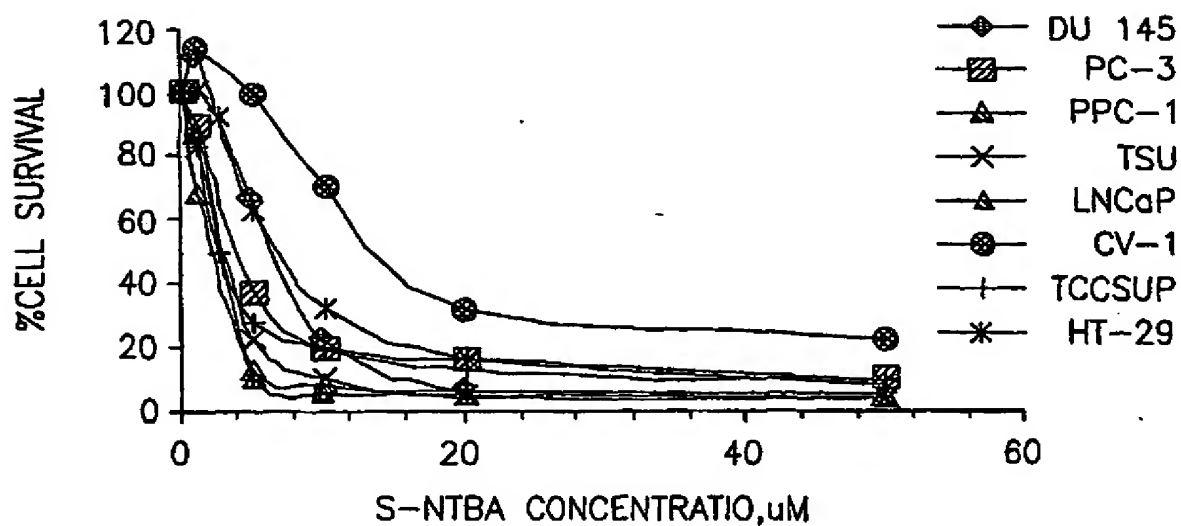


FIG. 1B

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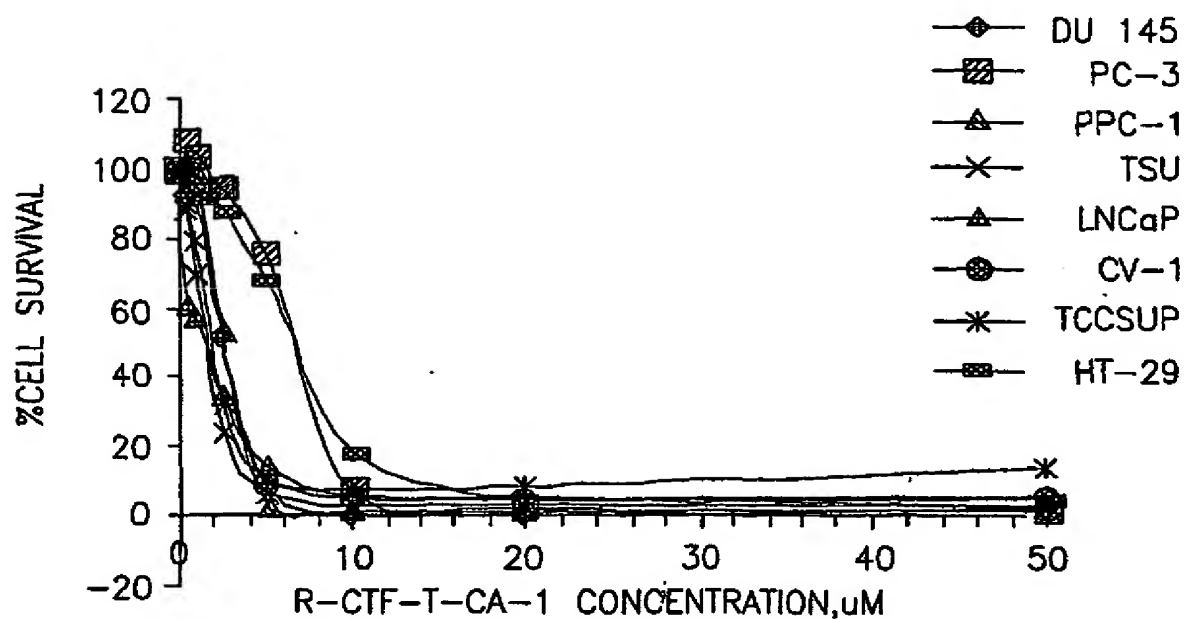


FIG. 1C

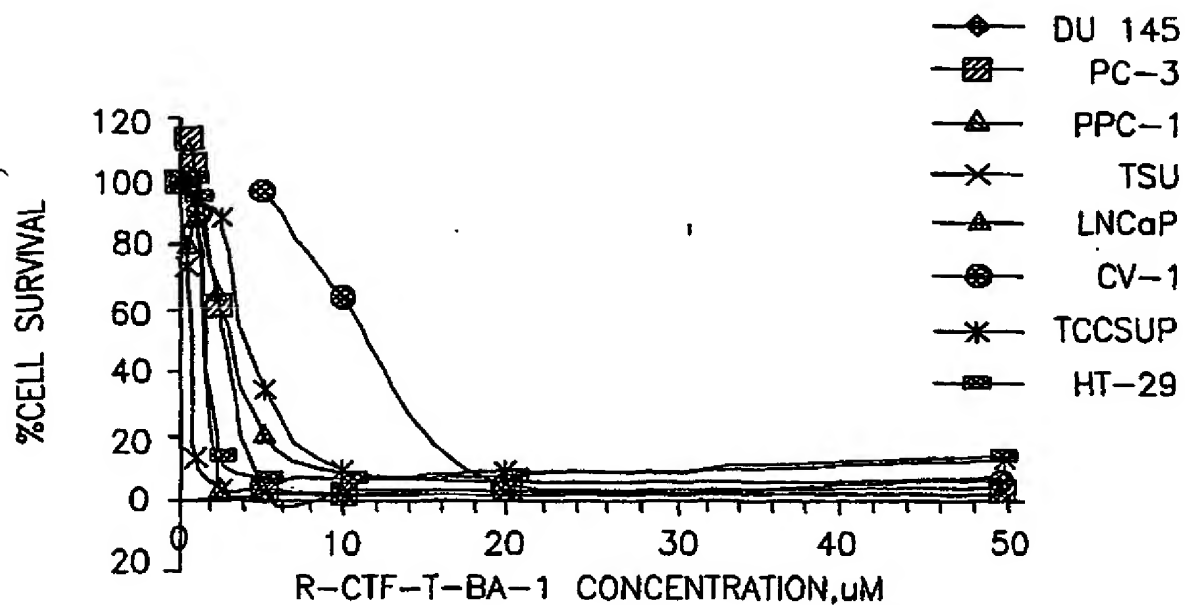


FIG. 1D

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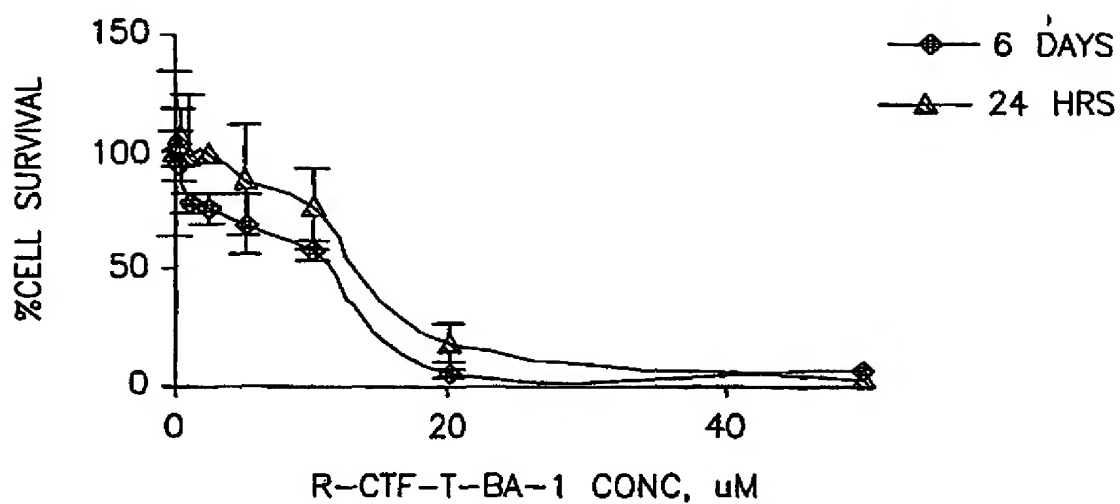


FIG.2A

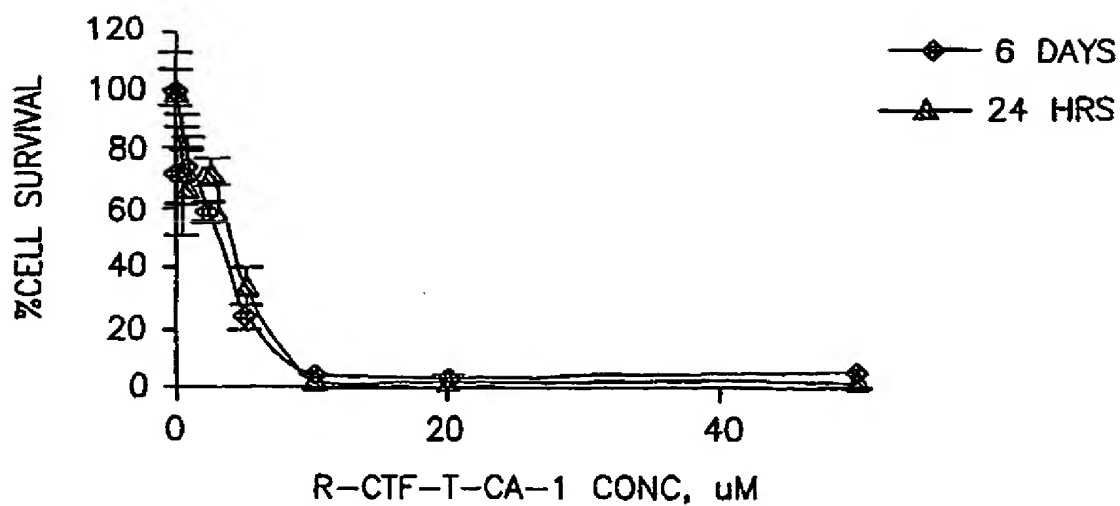


FIG.2B

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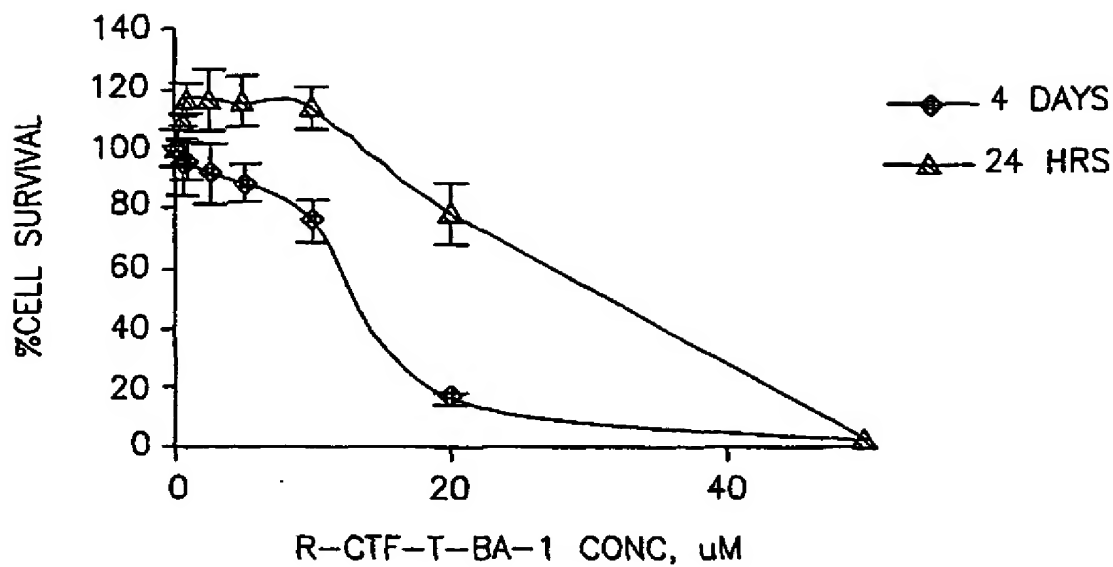


FIG.3A

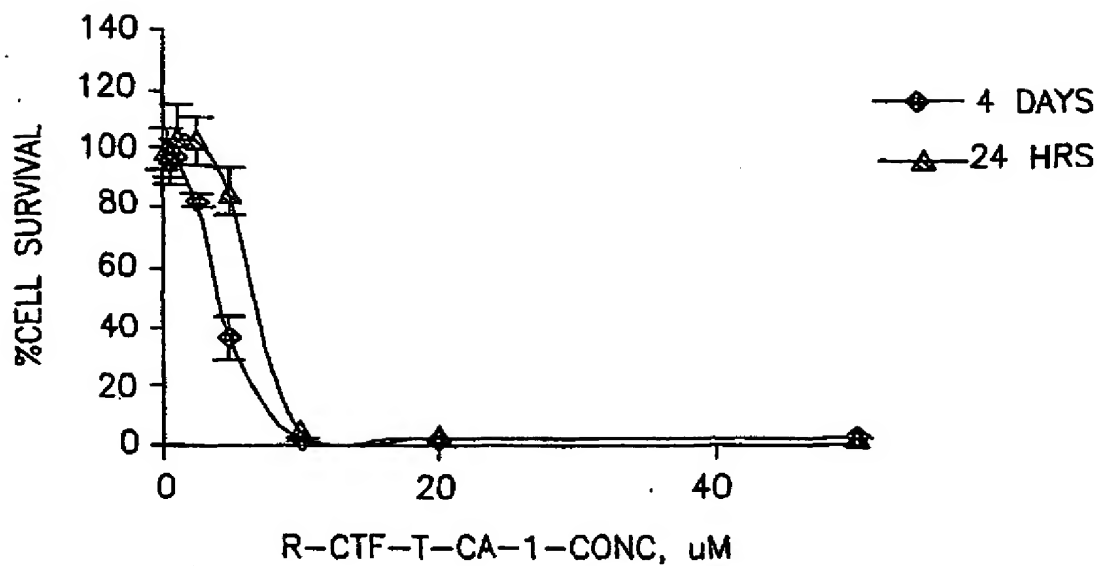


FIG.3B

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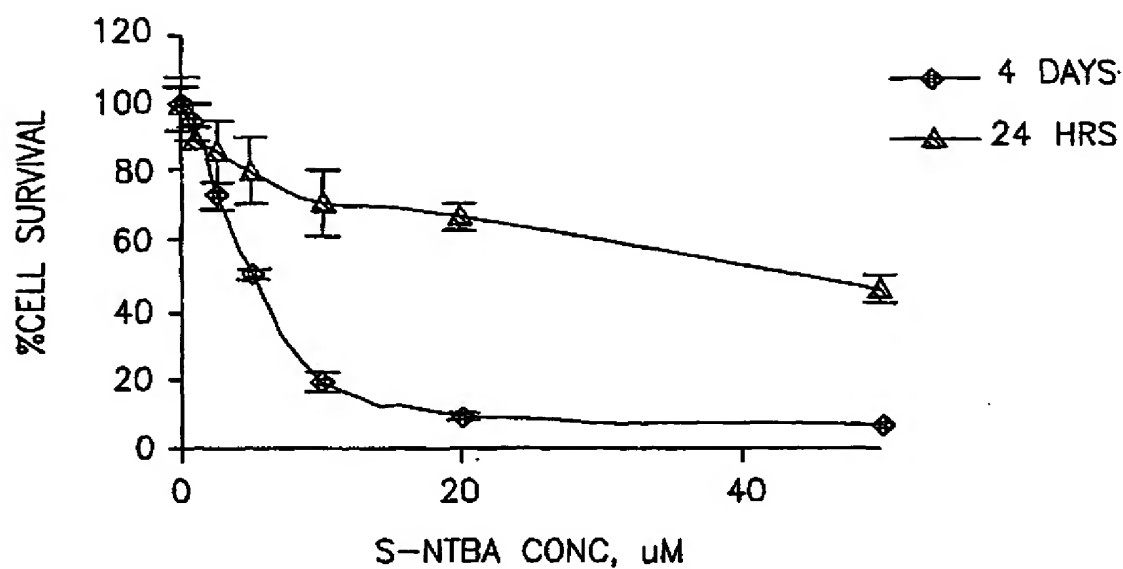


FIG.3C

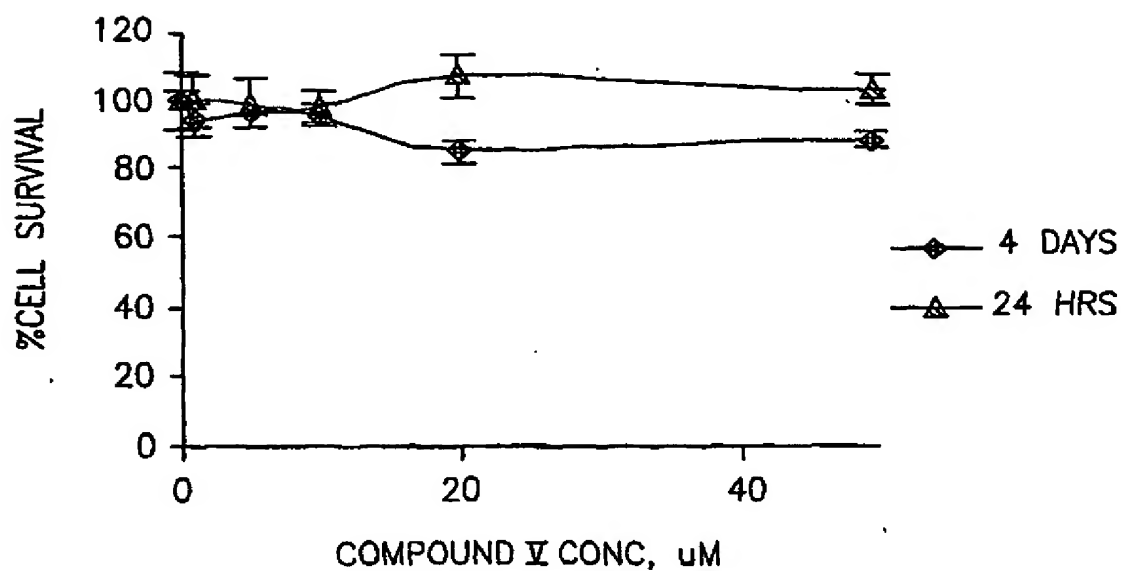


FIG.3D

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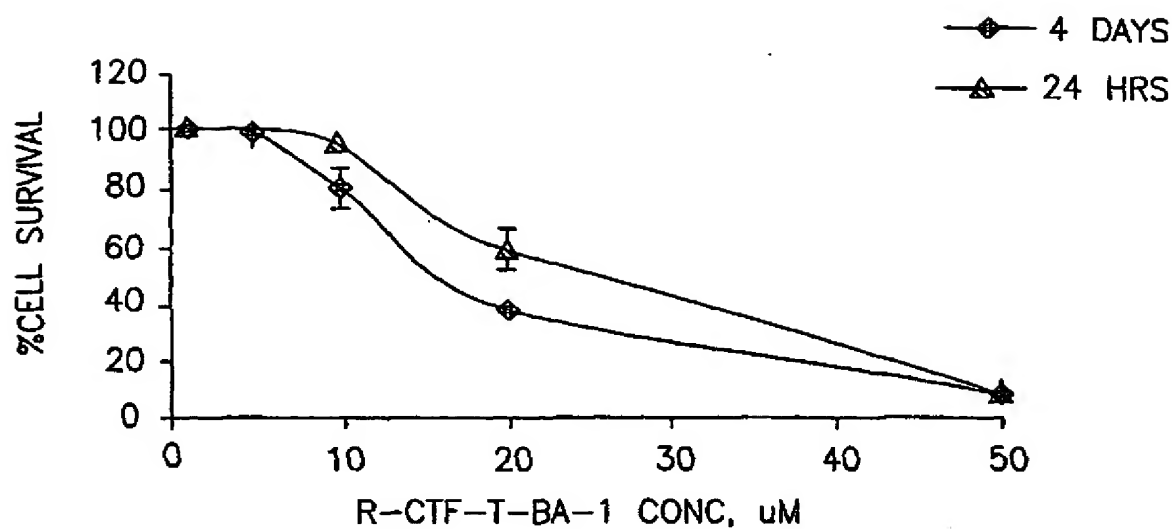


FIG.4A

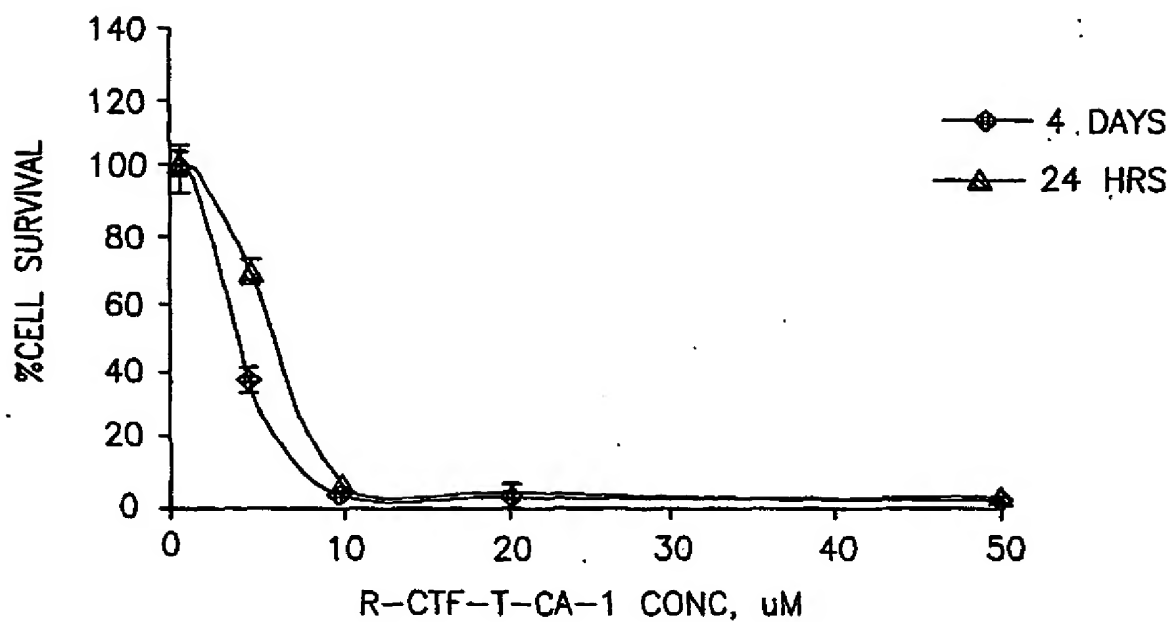


FIG.4B

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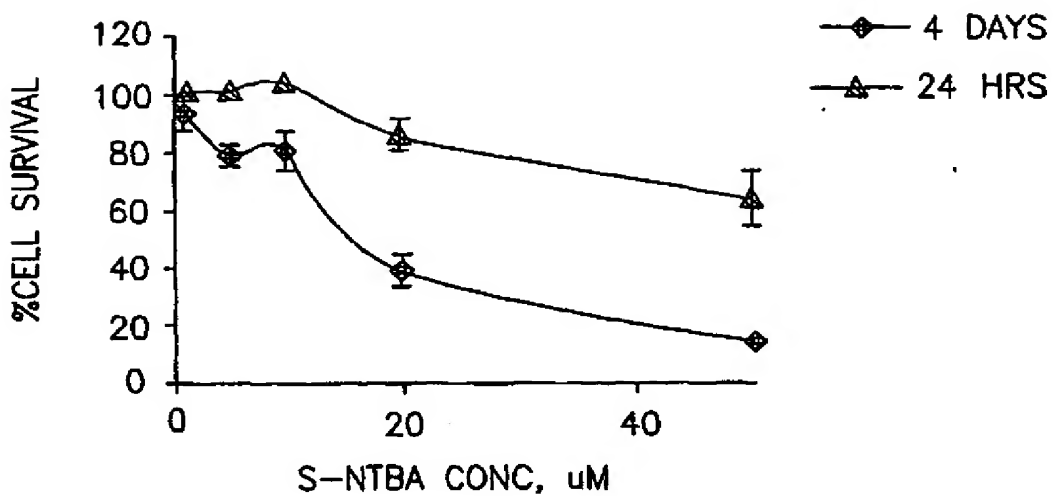


FIG.4C

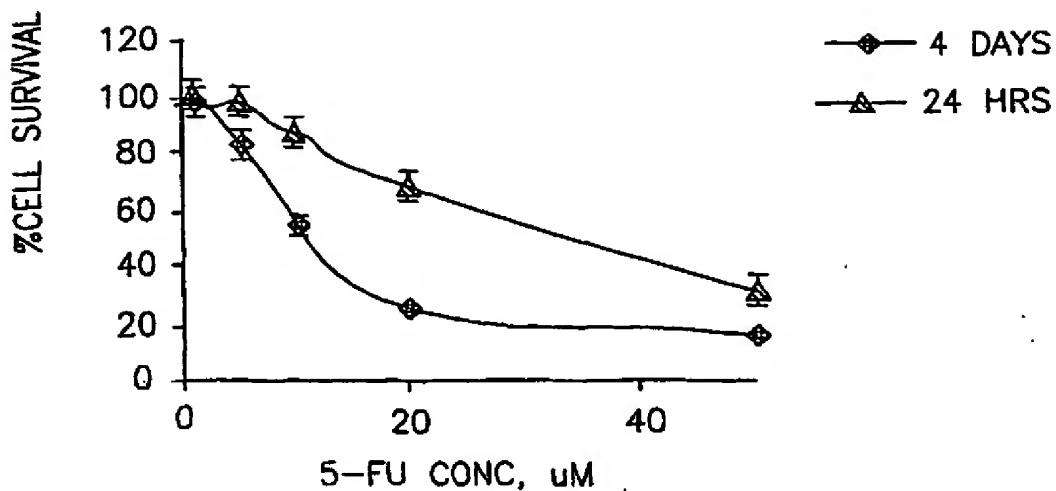


FIG.4D

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Cove, S., Cordova, TN 38018 (US).

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LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
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ning of each regular issue of the PCT Gazette.

(54) Title: IRREVERSIBLE SELECTIVE ANDROGEN RECEPTOR MODULATORS AND METHODS OF USE THEREOF

(57) Abstract: In one embodiment, this invention provides a class of androgen receptor targeting agents (ARTA). The agents define a new subclass of compounds, which are selective androgen receptor modulators (SARM). The SARM compounds have unexpected antiandrogenic activity of a nonsteroidal ligand for the androgen receptor. In one embodiment, the SARM compounds bind irreversibly to the androgen receptor. In another embodiment, the SARM compounds are androgen receptor antagonists which bind irreversibly to the androgen receptor. In another embodiment, the SARM compounds are alkylating agents. The SARM compounds, either alone or as a composition, are useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with Androgen Decline in Aging Male (ADAM), such as fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, anemia, obesity, sarcopenia, osteopenia, osteoporosis, benign prostate hyperplasia, alterations in mood and cognition and prostate cancer; c) treatment of conditions associated with Androgen Decline in Female (ADIF), such as sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian cancer; d) treatment and/or prevention of acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; g) decreasing the incidence of, halting or causing a regression of prostate cancer; and/or h) inducing apoptosis in a cancer cell.

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/03121

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 6,071,957 A (MILLER et al) 06 June 2000(06.06.2000), column 7-8, compound 10, , column 17-18, scheme 1, and column 3, lines 1-45.	1-1-5, 7-10, 12-19, 21-24, 26-33, 35-38, 40-76 ----- 1-77

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

01 MAY 2003


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